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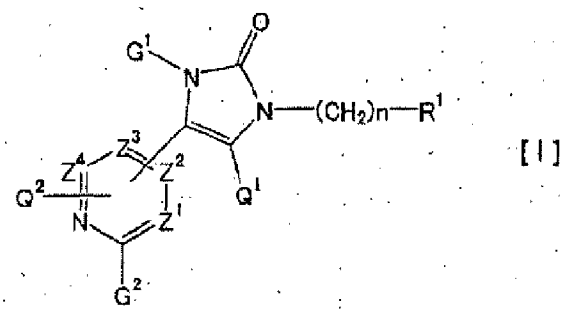
(54) 4-IMIDAZOLIN-2-ONE COMPOUNDS

(57) The present invention relates to a compound of the formula [I]:



[I]

wherein G^1 is an alkyl which,may be substituted by a halogen atom or an alkoxy, or a group of the formula:

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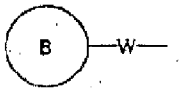


wherein ring B is benzene ring which may be substituted, etc.,

Q^1 and Q^2 may be the same or different, and each is hydrogen atom, a halogen atom or an alkyl,

n is 0, 1, 2, 3 or 4,

R^1 is hydrogen atom, an alkyl which may be substituted, a cycloalkyl which may be substituted, a phenyl which may be substituted, etc.,

Z^1, Z^2, Z^3 and Z^4 may be the same or different, and each is CH or N, provided that 3 or more of Z^1, Z^2, Z^3 and Z^4 should not be N at the same time,

G^2 is hydrogen atom, $-NR^3R^4$, $-OR^5$, etc., where R^3 to R^8 each is independently hydrogen atom, an alkyl which may be substituted, an alkenyl, an alkynyl, etc.,

or a pharmaceutically acceptable salt thereof.

Description

Technical Field

[0001] The present invention relates to a novel 4-imidazolin-2-one compound which has an excellent p38MAP kinase inhibitory action and is useful for a medicament.

Background Art

[0002] Mitogen-activated protein (MAP) kinase is a member of serine-threonine kinases which transfers a γ-phosphate group of adenosine triphosphate (ATP) to a hydroxy of specific serine or threonine which constitutes a protein, and is involved in various cellular responses against extracellular signals. p38 MAP kinase is an about 38 kDa protein and cloned as a homologue of MAP kinases.

[0003] p38MAP kinase is activated by inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin 1 (IL-1), and by stimulation caused by stress such as ultraviolet irradiation. p38 MAP kinase recognizes various transcription factors and protein kinases as a substrate. It has been clearly shown that, being activated by p38 MAP kinase, these transcription factors and protein kinases become involved in promoting transcription, post-transcriptional regulation (e.g. stabilizing mRNA and promoting protein translation) or stabilizing proteins, etc. of various proteins including inflammatory cytokines, which are involved in inflammatory reactions. From these findings, it is thought that p38 MAP kinase is critically involved in the various inflammatory reactions by regulating the production and the signal transduction of inflammatory cytokines, and an inhibitor of p38 MAP kinase can highly expected to serve as a therapeutic agent for various diseases including inflammatory diseases.

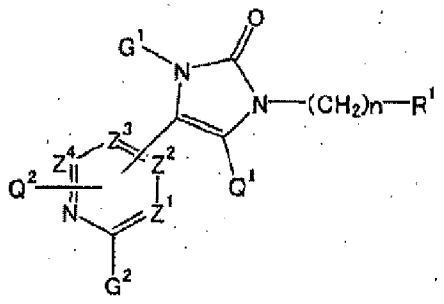
[0004] As the inhibitors for p38 MAP kinase, there have been disclosed imidazole derivatives in PCT Japanese Provisional Patent Publication No.2000-503304, 1,3-thiazole derivatives in Japanese Provisional Patent Publication No. 2001-114690, 1,3-thiazole derivatives and 1,3-oxazole derivatives in Japanese Provisional Patent Publication No. 2001-114779, imidazole derivatives, pyrrole derivatives, furan derivatives, 3-pyrazolin-5-one derivatives, pyrazole derivatives and thiophene derivative, etc. in Expert Opinion on Therapeutic Patents (2000) 10(1) : 25-37, respectively. However, there has been no description on 4-imidazolin-2-one derivatives in any of these.

[0005] An object of the present invention is to provide a novel compound having an excellent p38 MAP kinase inhibitory action and is useful as a pharmaceutical.

Disclosure of Invention

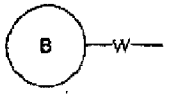
[0006] The present inventions are as disclosed as follows.

[1] A compound of the formula [I]:



[I]

wherein G^1 is an alkyl which may be substituted by a halogen atom or an alkoxy, or a group of the formula:



wherein ring B is benzene ring, naphthalene ring, a monocyclic or bicyclic aromatic heterocycle or a cycloalkane, and the benzene ring, the naphthalene ring, the monocyclic or bicyclic aromatic heterocycle and the

cycloalkane may be substituted by 1 to 3 substituent(s), which is(are) the same or different, and selected from the group consisting of a halogen atom, nitro, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted amino, an optionally substituted carbamoyl and cyano, W is a single bond, or a c_1 - c_4 alkylene which may be substituted by 1 or 2 alkyl(s),

Q^1 and Q^2 may be the same or different, and each is hydrogen atom, a halogen atom or an alkyl,

n is 0, 1, 2, 3 or 4,

R^1 is hydrogen atom, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted phenyl or an optionally substituted heterocyclic group,

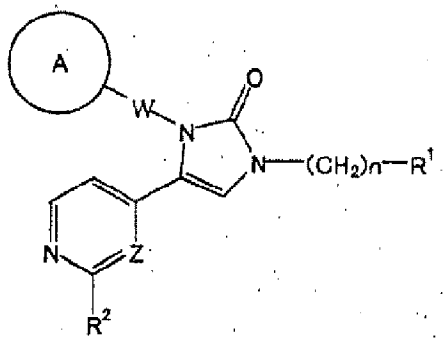
Z^1, Z^2, Z^3 and Z^4 may be the same or different, and each is CH or N, provided that 3 or more of Z^1, Z^2, Z^3 and Z^4 should not be N at the same time,

G^2 is hydrogen atom, $-NR^3R^4$, $-OR^5$, $-SR^5$ $-COR^6$, $-CHR^7R^8$, or a heterocyclic group,

where R^3 to R^8 each independently is hydrogen atom, an optionally substituted alkyl, an alkenyl, an alkynyl, hydroxy, an alkoxy, an optionally substituted amino, an optionally substituted alkanoyl, an optionally substituted carbamoyl, an alkoxyoxalyl, an alkylsulfonyl, an optionally substituted cycloalkyl, an optionally substituted phenyl, an optionally substituted heterocyclic group, a carbonyl substituted by an optionally substituted cycloalkyl, a carbonyl substituted by an optionally substituted phenyl or a carbonyl substituted by an optionally substituted heterocyclic group,

or a pharmaceutically acceptable salt thereof.

[2] A compound of the formula [Ia]:



[Ia]

wherein ring A is benzene ring or a monocyclic aromatic heterocycle, and the benzene ring and the monocyclic aromatic heterocycle may be substituted by 1 to 3 substituent(s), which is(are) the same or different, and selected from the group consisting of a halogen atom, nitro, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted amino, an optionally substituted carbamoyl and cyano,

W is a single bond, or a c_1 - c_4 alkylene which may be substituted by 1 or 2 alkyl(s),

n is 0, 1, 2, 3 or 4,

R^1 is hydrogen atom, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted phenyl or an optionally substituted heterocyclic group,

Z is CH or N,

R^2 is hydrogen atom, $-NR^3R^4$, $-OR^5$, $-COR^6$ or $-CHR^7R^8$,

where R^3 to R^8, each independently is hydrogen atom, an optionally substituted alkyl, an alkenyl, an alkynyl, hydroxy, an alkoxy, an optionally substituted amino, an optionally substituted alkanoyl, an optionally substituted carbamoyl, an alkoxyoxalyl, an alkylsulfonyl, an optionally substituted cycloalkyl, an optionally substituted phenyl, an optionally substituted heterocyclic group, a carbonyl substituted by an optionally substituted cycloalkyl, a carbonyl substituted by an optionally substituted phenyl or a carbonyl substituted by an optionally substituted heterocyclic group,

or a pharmaceutically acceptable salt thereof.

[3] The compound according to [2], wherein the ring A is a benzene ring which may be substituted by 1 to 3 substituent (s), which is (are) the same or different, and selected from the group consisting of a halogen atom, nitro, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted amino and cyano, and W is a single bond, or a pharmaceutically acceptable salt thereof.

[4] The compound according to [2] or [3], wherein n is 0 or 1, or a pharmaceutically acceptable salt thereof

[5] The compound according to any one of [2] to [4], wherein n is 0 and R^1 is an optionally substituted alkyl, or n is 1 and R^1 is an optionally substituted cycloalkyl or an optionally substituted phenyl, or a pharmaceutically ac-

ceptable salt thereof.

[6] The compound according to any one of [2] to [5], wherein R^2 is $-NR^3R^4$ or $-OR^5$, or a pharmaceutically acceptable salt thereof.

[7] The compound according to any one of [2] to [5], wherein R^2 is $-NHR^4$, and R^4 is an optionally substituted alkyl, an alkenyl, an optionally substituted alkanoyl, an optionally substituted carbamoyl, an optionally substituted cycloalkyl, an optionally substituted phenyl, an optionally substituted heterocyclic group, a carbonyl substituted by an optionally substituted cycloalkyl or a carbonyl substituted by an optionally substituted heterocyclic group, or a pharmaceutically acceptable salt thereof.

[8] The compound according to [2], wherein the ring A is a benzene ring which may be substituted by 1 or 2 substituent(s), which is(are) the same or different, and selected from the group consisting of a halogen atom, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted amino and cyano,
W is a single bond,
n is 0 or 1,
R^1 is hydrogen atom, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted phenyl or an optionally substituted heterocyclic group,
Z is CH or N,
R^2 is hydrogen atom, $-NR^3R^4$, $-OR^5$, $-COR^6$ or $-CHR^7R^8$,
where R^3 to R^8 each independently is hydrogen atom, an optionally substituted alkyl, an alkenyl, an alkoxy, an optionally substituted alkanoyl, an optionally substituted carbamoyl, an alkoxyoxalyl, an optionally substituted cycloalkyl, an optionally substituted phenyl, an optionally substituted heterocyclic group, a carbonyl substituted by an optionally substituted cycloalkyl or a carbonyl substituted by an optionally substituted heterocyclic group,
or a pharmaceutically acceptable salt thereof.

[9] The compound according to [2], wherein the ring A is a benzene ring which may be substituted by 1 or 2 substituent(s), which is(are) the same or different, and selected from the group consisting of a halogen atom, an alkyl, an alkoxy, an amino optionally substituted by alkyl(s) and cyano,
W is a single bond,
n is 0 or 1,
R^1 is

(1) hydrogen atom,
(2) an alkyl optionally substituted by group(s) selected from the group consisting of phenyl, an alkoxy, an alkylamino, a dialkylamino, an alkanoylamino, an alkylsulfonylamino, a carbamoyl which may be substituted by alkyl(s), hydroxy, carboxy and cyano,
(3) a cycloalkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (v):

(i) hydroxy,
(ii) an alkoxy optionally substituted by alkoxy(s),
(iii) an amino optionally substituted by group(s) selected from the group consisting of an alkyl, an alkanoyl and an alkylsulfonyl,
(iv) a carbamoyl optionally substituted by alkyl(s), and
(v) an alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, an alkoxy and amino,

(4) a phenyl optionally substituted by group(s) selected from the group consisting of the following (i) to (vi):

(i) a halogen atom,
(ii) an alkyl optionally substituted by group(s) selected from the group consisting of a halogen atom, hydroxy and phenylsulfonyl,
(iii) cyano,
(iv) an alkoxy,
(v) an amino optionally substituted by group(s) selected from the group consisting of an alkyl and an alkylsulfonyl,
(vi) a carbonyl substituted by a heterocyclic group, or

(5) a heterocyclic group optionally substituted by group(s) selected from the group consisting of the following (i) to (iv):

(i) an alkoxycarbonyl,

(ii) an alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, an alkoxy and a carbamoyl optionally substituted by alkyl(s),
(iii) an alkanoyl and
(iv) an alkylsulfonyl,

Z is CH or N,
R^2 is hydrogen atom, $-NR^3R^4$, $-OR^5$, $-COR^6$ or $-CHR^7R^8$,
where R^3 to R^8 each independently is:

(1) hydrogen atom,
(2) an alkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (vii):

(i) hydroxy,
(ii) an alkoxy,
(iii) an amino optionally substituted by group(s) selected from the group consisting of an alkyl, an alkanoyl and an alkylsulfonyl,
(iv) an alkoxycarbonyl,
(v) a cycloalkyl optionally substituted by group(s) selected from the group consisting of the following a) to g):

a) hydroxy,
b) an amino optionally substituted by alkyl(s),
c) an alkanoylamino,
d) an alkylsulfonylamino,
e) an alkyl optioinally substituted by group(s) selected from the group consisting of hydroxy, an alkoxy, amino, a carbamoyl optionally substituted by alkyl(s),
f) carboxy and
g) a carbamoyl optionally substituted by alkyl(s),

(vi) a phenyl optionally substituted by group(s) selected from the group consisting of a halogen atom, an alkoxy and morpholinylcarbonyl, and
(vii) a heterocyclic group optionally substituted by alkyl(s),

(3) an alkenyl,
(4) an alkoxy,
(5) an alkanoyl optionally substituted by group(s) selected from the group consisting of the following (i) to (iv):

(i) hydroxy,
(ii) an alkoxy,
(iii) an amino optionally substituted by group(s) selected from the group consisting of an alkyl and an alkanoyl,
(iv) an alkoxycarbonyl,

(6) a carbamoyl optionally substituted by alkyl(s),
(7) an alkoxyoxalyl,
(8) a cycloalkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (vii):

(i) a halogen atom,
(ii) hydroxy,
(iii) an alkoxy,
(iv) an amino optionally substituted by group(s) selected from the group consisting of an alkyl, an alkanoyl, an alkoxycarbonyl and an alkylsulfonyl,
(v) an alkyl optionally substituted by group (s) selected from the group consisting of hydroxy, an alkoxy, amino, a carbamoyl optionally substituted by alkyl(s),
(vi) an alkanoyloxy and
(vii) a carbamoyl optionally substituted by alkyl(s),

(9) a phenyl optionally substituted by group(s) selected from the group consisting of a halogen atom and an

alkoxy,
(10) a heterocyclic group optionally substituted by group(s) selected from the group consisting of the following (i) to (v):

(i) an alkyl optionally substituted by group(s) selected from the group consisting of phenyl, hydroxy, an alkoxy, amino and a carbamoyl optionally substituted by alkyl(s),
(ii) an alkoxycarbonyl,
(iii) an alkanoyl,
(iv) an alkylsulfonyl,
(v) oxo

(11) a carbonyl substituted by a cycloalkyl optionally substituted by group(s) selected from the group consisting of hydroxy, amino and an alkanoylamino, or
(12) a heterocyclic group-substituted carbonyl,

or a pharmaceutically acceptable salt thereof.
[10] The compound according to [2], wherein the ring A is a benzene ring which may be substituted by 1 or 2 substituent(s), which is(are) the same or different, and selected from the group consisting of fluorine atom, chlorine atom, an alkyl and an alkoxy,
W is a single bond,
n is 0 or 1,
R^1 is

(1) hydrogen atom,
(2) an alkyl optionally substituted by group(s) selected from the group consisting of phenyl, an alkoxy, an alkylamino, a dialkylamino, an alkanoylamino, an alkylsulfonylamino, a carbamoyl optionally substituted by alkyl(s), hydroxy, carboxy and cyano,
(3) a cycloalkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (v):

(i) hydroxy,
(ii) an alkoxy optionally substituted by alkoxy(s),
(iii) an amino optionally substituted by group(s) selected from the group consisting of an alkyl, an alkanoyl and an alkylsulfonyl,
(iv) a carbamoyl optionally substituted by alkyl(s),
(v) an alkyl optionally substituted by group(s) selected from the group consisting of hydroxy and amino,

(4) a phenyl optionally substituted by group(s) selected from the group consisting of the following (i) to (iv):

(i) a halogen atom,
(ii) an alkyl optionally substituted by halogen atom(s),
(iii) cyano, and
(iv) an alkoxy, or

(5) a heterocyclic group,

Z is CH or N,
R^2 is hydrogen atom, $-NR^3R^4$, $-OR^5$, or $-COR^6$,
where R^3 to R^6 each independently is:

(1) hydrogen atom,
(2) an alkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (vi) :

(i) hydroxy,
(ii) an alkoxy,
(iii) an alkoxycarbonyl,
(iv) a cycloalkyl optionally substituted by group(s) selected from the group consisting of the following a) to e) :

a) hydroxy,
b) an amino optionally substituted by alkyl(s),
c) an alkanoylamino,
d) an alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, amino and a carbamoyl optionally substituted by alkyl(s), and
e) a carbamoyl optionally substituted by alkyl(s),

(v) a phenyl optionally substituted by alkoxy(s), and
(vi) a heterocyclic group,

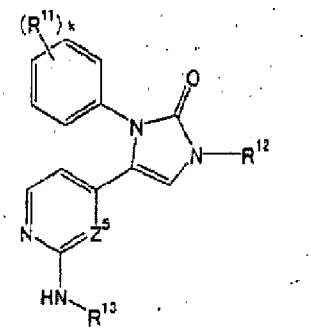
(3) an alkenyl,
(4) an alkoxy,
(5) an alkanoyl optionally substituted by group(s) selected from the group consisting of an alkoxy, an amino optionally substituted by alkanoyl(s), and an alkoxycarbonyl,
(6) a cycloalkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (v):

(i) hydroxy,
(ii) an alkoxy,
(iii) an amino optionally substituted by group(s) selected from the group consisting of an alkyl, an alkanoyl, an alkoxycarbonyl and an alkylsulfonyl,
(iv) an alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, amino and a carbamoyl optionally substituted by alkyl(s),
(v) a carbamoyl optionally substituted by alkyl(s),

(7) a heterocyclic group optionally substituted by group(s) selected from the group consisting of an alkyl optionally substituted by phenyl(s) and an alkoxycarbonyl,
(8) a carbonyl substituted by a cycloalkyl optionally substituted by group(s) selected from the group consisting of hydroxy and amino, or
(9) a heterocyclic group-substituted carbonyl,

or a pharmaceutically acceptable salt thereof.

[11] A compound of the formula [Ib]:



wherein R^{11} is a group selected from the group consisting of hydrogen atom, a halogen atom, a c_1 - c_4 alkyl, and a c_1 - c_4 alkoxy,
k is 1 or 2, and when k is 2, two of R^{11}s may be the same or different,
R^{12} is

(1) a c_1 - c_4 alkyl,
(2) a c_3 - c_4 cycloalkylmethyl,
(3) carbamoylmethyl, or
(4) a benzyl optinally substituted by group(s) selected from the group consisting of cyano, a halogen atom, a c_1 - c_3 alkoxy, a c_1 - c_3 alkyl and a halogen-substituted c_1 - c_3 alkyl,

Z^5 is CH or N,

R^{13} is

(1) a c_1 - c_6 alkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (iii):

(i) a c_5 - c_7 cycloalkyl optionally substituted by group(s) selected from the group consisting of the following a) to e):

a) hydroxy
b) an amino optionally substituted by c_1- c_4 alkyl(s),
c) a c_1 - c_4 alkanoylamino,
d) a c_1 - c_4 alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, amino, and a carbamoyl optionally substituted by c_1 - c_4 alkyl(s), and
e) a carbamoyl which may be substituted by c_1 - c_4 alkyl(s),

(ii) hydroxy, and
(iii) a carbamoyl optionally substituted by c_1 - c_4 alkyl(s), or

(2) a c_5- c_7 cycloalkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (iii):

(i) hydroxy,
(ii) a c_1- c_4 alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, amino and a carbamoyl optionally substituted by c_1 - c_4 alkyl(s), and
(iii) a carbamoyl optionally substituted by c_1 - c_4 alkyl(s),

or a pharmaceutically acceptable salt thereof.

[12] The compound according to [11], wherein R^{11} is a group selected from the group consisting of hydrogen atom, fluorine atom, chlorine atom, methyl and methoxy,
k is 1 or 2, and when k is 2, two of R^{11}s may be the same or different,
R^{12} is a c_1 - c_4 alkyl, cyclopropylmethyl or carbamoylmethyl, or a pharmaceutically acceptable salt thereof.

[13] The compound according to [11], wherein R^{11} is hydrogen atom or fluorine atom,
k is 1,
R^{12} is ethyl, isopropyl, isobutyl, cyclopropylmethyl or carbamoylmethyl,
R^{13} is

(1) a c_1 - c_6 alkyl optionally substituted by group(s) selected from the group consisting of the following (i) and (ii):

(i) a c_5 - c_7 cycloalkyl optionally substituted by group(s) selected from the group consisting of hydroxy, a hydroxy c_1 - c_4 alkyl and a carbamoyl optionally substituted by c_1 - c_4 alkyl(s), and
(ii) hydroxy, or

(2) a c_5 - c_7 cycloalkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (iii):

(i) hydroxy,
(ii) a c_1 - c_4 alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, amino and a carbamoyl optionally substituted by c_1 - c_4 alkyl(s),
(iii) a carbamoyl optionally substituted by c_1 - c_4 alkyl(s),

or a pharmaceutically acceptable salt thereof.

[14] A meidcament comprising the compound according to any one of [1] to [13], or a pharmaceutically acceptable salt thereof.

[15] A p38 MAP kinase inhibitory agent comprising, as an effective ingredient, the compound according to any one of [1] to [13], or a pharmaceutically acceptable salt thereof.

[16] An agent for prophylaxis or treatment of an inflammatory disease comprising, as an effective ingredient, the compound according to any one of [1] to [13], or a pharmaceutically acceptable salt thereof.

[17] An agent for prophylaxis or treatment according to [16], wherein the inflammatory disease is arthritis.

Best Mode for Carrying out the Invention

[0007] In the present invention, "an alkyl" and alkyls in "an alkylthio", "an alkylsulfinyl" and "an alkylsulfonyl" are exemplified by a straight or branched chain C_1-C_6 alkyl, and specifically, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, etc. Preferred is a c_1-$c_4$alkyl.

[0008] "An alkoxy" and alkoxys in "an alkoxycarbonyl" and "an alkoxyoxalyl" are exemplified by a straight and branched chain C_1-C_6 alkoxy, and specifically, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, hexoxy, etc. Preferred is a C_1-C_4alkoxy.

[0009] "An alkenyl" is exemplified by a straight or branched chain C_2-C_7alkenyl, and specifically, vinyl, allyl, 3-butenyl, 2-pentenyl, 3-hexenyl, etc. Preferred is a C_2-C_5 alkenyl, etc.

[0010] "An alkynyl" is exemplified by a straight or branched chain C_2-C_7 alkynyl, and specifically, ethynyl, propargyl, 3-butynyl, 2-pentynyl, 3-hexynyl, etc. Preferred is a C_2-C_5 alkynyl.

[0011] "An alkanoyl" is exemplified by a straight or branched chain C_2-C_7 alkanoyl, and specifically, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, hexanoyl, etc. Preferred is a C_2-C_5 alkanoyl.

[0012] "A cycloalkyl" is exemplified by a C_3-C_8 cycloalkyl, and preferred is a C_3-C_6 cycloalkyl.

[0013] "A cycloalkane" is exemplified by a C_3-C_8 cycloalkane, and preferred is a C_5-C_7 cycloalkane.

[0014] "A halogen atom" is exemplified by fluorine atom, chlorine atom, bromine atom, iodine atom, and preferred are fluorine atom and chlorine atom.

[0015] "A heterocyclic group" is exemplified by a partially or completely saturated monocyclic, bicyclic or tricyclic heterocyclic group containing 1 to 3 heteroatoms selected from nitrogen atom, oxygen atom, and sulfur atom. Preferred is a 5- or 6-membered monocyclic heterocyclic group, and specific examples are furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, tetrazolyl, pyrrolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, piperidinyl, pyrazolyl, piperazinyl, morpholinyl, imidazolyl, triazolyl, imidazolinyl, pyrazolinyl, etc.

[0016] "A monocyclic or bicyclic aromatic heterocycle" is exemplified by a monocyclic or bicyclic aromatic heterocycle containing 1 to 3 heteroatoms selected from nitrogen atom, oxygen atom, and sulfur atom. Additionally, "monocyclic aromatic heterocycle" is exemplified by a monocyclic aromatic heterocycle containing 1 to 3 heteroatoms selected from nitrogen atom, oxygen atom, and sulfur atom, for example, 5-or 6-membered monocyclic aromatic heterocycle. Specific examples for the monocyclic and bicyclic aromatic heterocycle include thiophene, furan, furazane, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, oxadiazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, quinazoline, isoquinoline, phthalazine, naphthyridine, quinazoline, quinoline, chromene, indolizine, isoindole, indole, purine, benzofuran, benzothiophene, etc. Preferred monocyclic aromatic heterocycles are thiophene, furan, etc.

[0017] When a substituent of the ring B in the compound [I] or a substituent of the ring A in the compound [Ia] is "an optionally substituted alkyl", examples for substituent of the alkyl include a halogen atom, hydroxy, amino, etc. The said alkyl may have 1 to 3 substituents mentioned above, and when the number of the substituents is two or more, each of the substituents may be the same or different. Specific examples for the substituted alkyl include hydroxymethyl, trifluoromethyl, aminomethyl, chloroethyl, etc.

[0018] When a substituent of the ring B or a substituent of the ring A is "an optionally substituted alkoxy", examples for substituent of the alkoxy include hydroxy, amino, etc. The said alkoxy may have 1 to 3 substituents mentioned above, and when the number of the substituents is two or more, each of the substituents may be the same or different.

[0019] When a substituent of the ring B or a substituent of the ring A is "an optionally substituted amino", examples for the substituent of the amino include an alkyl (said alkyl may be substituted with 1 to 3 groups which are the same or different, selected from the group consisting of an alkoxy, amino and carboxy), an alkanoyl, etc. The said amino may have 1 or 2 substituents mentioned above, and when the number of the substituents is two, each of the substituents may be the same or different.

[0020] When a substituent of the ring B or a substituent of the ring A is "an optionally substituted carbamoyl", examples for the substituents of the carbamoyl include alkyl, etc. The said carbamoyl may have 1 or 2 substituents mentioned above, and when the number of the substituents is two, each of the substituents may be the same or different.

[0021] A substituent of the ring B in the compound [I] or a substituent of the ring A in the compound [Ia] is preferably exemplified by a halogen atom, nitro, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted amino, and cyano. Particularly preferred are a halogen atom, a c_1-$c_4$alkyl, a c_1-$c_4$alkoxy, etc., and specific examples are fluorine atom, chlorine atom, methyl, methoxy, etc.

[0022] When R^1 of the compound [I] and the compound [Ia] is "an optionally substituted alkyl", examples for substituent of the alkyl include an alkynyl, cyano, an alkoxy, hydroxy, amino (said amino may be substituted with 1 or 2 substituents selected from the group consisting of an alkyl, an alkanoyl, and an alkylsulfonyl.), carboxy, an alkoxycarbonyl, carbamoyl (said carbamoyl may be substituted with 1 or 2 alkyl(s).), phenyl, naphthyl, etc. The said alkyl may have 1 to 3 substituents mentioned above, and when the number of the substituents is two or more, each of the substituents may be the same or different. Specific examples for the substituents include cyano, an alkoxy, hydroxy,

amino, carboxy, a carbamoyl which may be substituted by an alkyl, phenyl, etc.

[0023] When R^1 is "an optionally substituted cycloalkyl", examples for the substituents of the cycloalkyl include (1) hydroxy, (2) an alkoxy (said alkoxy may be substituted by 1 to 3 alkoxy(s)), (3) amino (said amino may be substituted by 1 or 2 group(s), being the same or different, and selected from the group consisting of the following (i) to (v) : (i) an alkyl, (ii) an alkanoyl, (iii) an alkoxycarbonyl, (iv) carbamoyl (said carbamoyl may be substituted by 1 or 2 alkyl(s).), and(v) an alkylsulfonyl], (4) carboxy, (5) an alkyl (said alkyl may be substituted by a group selected form the group consisting of hydroxy, an alkoxy and amino), (6) a carbamoyl which may be substituted by alkyl(s), etc. The said cycloalkyl may have 1 to 3 substituents mentioned above, and when the number of the substituents is two or more, each of the substituents may be the same or different.

[0024] When R^1 is "an optionally substituted phenyl", examples for the substituents of the phenyl include (1) a halogen atom, (2) nitro, (3) an alkyl (said alkyl may be substituted by 1 to 3 group(s), being the same or different, selected from the group consisting of a halogen atom, hydroxy, amino, carboxy, and phenylsulfonyl), (4) an alkenyl, (5) cyano, (6) hydroxy, (7) an alkoxy (said alkoxy may be substituted by 1 to 3 group(s), being the same or different, and selected from the group consisting of a halogen atom, carboxy, an alkoxycarbonyl, carbamoyl, phenyl and morpholinylcarbonyl), (8) amino [said amino may be substituted with 1 or 2 group(s), being the same or different, and selected from the group consisting of the following (i) to (iv) : (i) an alkyl, (ii) an alkanoyl, (iii)carbamoyl (said carbamoyl may be substituted by 1 or 2 group(s), being the same or different, and selected from the group consisting of an alkyl and a cycloalkyl), and (iv) an alkylsulfonyl], (9) an alkanoyl, (10) carboxy, (11) an alkoxycarbonyl, (12)carbamoyl [said carbamoyl may be substituted by 1 or 2 group(s), being the same or different, and selected from the group consisting of the following (i) and (ii): (i) an alkyl (said alkyl may be substituted by 1 to 3 hydroxy(s)) and (ii) a cycloalkyl], (13) an alkylthio, (14) an alkylsulfinyl, (15) an alkylsulfonyl, (16) phenyl, (17) tetrazolyl, (18) a heterocyclic group-substituted carbonyl (said heterocyclic group may be substituted by 1 to 3 group(s) , being the same or different, and selected from the group consisting of an alkyl and an alkoxycarbonyl), etc. When R^1 is an optionally substituted phenyl, said phenyl may have 1 to 3 substituent(s) mentioned above, and when the number of the substituents is 2 or more, each of the substituents may be the same or different. Preferred substituents are (1) a halogen atom, (2) an alkyl (said alkyl may be substituted by 1 to 3 group(s), being the same or different, and selected from the group consisting of a halogen atom, hydroxy, amino, carboxy, and phenylsulfonyl), (3) cyano, (4) an alkoxy (said alkoxy may be substituted by 1 to 3 group(s), being the same or different, and selected from the group consisting of a halogen atom, carboxy, an alkoxycarbonyl, carbamoyl, phenyl and morpholinyl carbonyl), etc. There is no limitation regarding positions of the substituents, as long as it is possible to substitute, and a particularly preferred position is 2-position.

[0025] When R^1 is "a phenyl substituted by a heterocyclic group-substituted carbonyl", examples for the heterocyclic group include the above-mentioned heterocyclic groups, and preferred are 5- or 6-membered monocyclic nitrogen-containing aliphatic heterocyclic groups. Specific examples are pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, etc.

[0026] When R^1 is "an optionally substituted heterocyclic group", examples for the heterocyclic group include the above-mentioned heterocyclic groups, and preferred are 5- or 6-membered monocyclic heterocyclic groups. Specific examples are furyl, tetrahydrofuryl, thienyl, thiazolyl, isoxazolyl, oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, piperidinyl, pyrrolidinyl, pyrazolyl, tetrazolyl, tetrahydropyranyl, etc. Particularly preferred are piperidinyl, tetrahydropyranyl, etc. Further, the substituents of the heterocyclic group are exemplified by a halogen atom, nitro, an alkyl (said alkyl may be substituted by a group selected from the group consisting of hydroxy, an alkoxy, a carbamoyl which may be substituted by alkyl(s) and carboxy(s)), cyano, hydroxy, amino, an alkanoyl, carboxy, an alkoxycarbonyl, carbamoyl (said carbamoyl may be substituted by 1 or 2 alkyl(s)), an alkylsulfonyl, phenyl, etc. The said heterocyclic group may have 1 to 3 substituent(s) mentioned above, and when the number of the substituents is 2 or more, each of the substituents may be the same or different.

[0027] A preferred combination of n and R^1 in the compound [I] and the compound [Ia] are exemplified by (1) those in which n is 0 and R^1 is an optionally substituted alkyl, (2) those in which n is 1 and R^1 is an optionally substituted cycloalkyl, (3) those in which n is 1 and R^1 is an optionally substituted phenyl, and (4) those in which n is 1 and R^1 is an optionally substituted heterocyclic group, etc. Particularly preferred are (1) those in which n is 0 and R^1 is an optionally substituted alkyl, (2) those in which n is 1 and R^1 is an optionally substituted phenyl, etc. Further preferred are (1) those in which n is 0 and R^1 is a C_1-C_4 alkyl, (2) those in which n is 1 and R^1 is a phenyl (said phenyl may be substituted by a group selected from the group consisting of cyano, fluorine atom, chlorine atom and methyl), etc.

[0028] When R^3 to R^8 in the compound [I] and the compound [Ia] is "an optionally substituted alkyl", the substituents of the alkyl are exemplified by (1) hydroxy, (2) an alkoxy group, (3) amino (said amino may be substituted by 1 or 2 group(s), being the same or different, and selected from the group consisting of an alkyl, an alkanoyl and an alkylsulfonyl), (4) an alkoxycarbonyl, (5) a cycloalkyl [said cycloalkyl may be substituted by 1 to 3 group(s), being the same or different, and selected from the group consisting of hydroxy, an amino which may be substituted by alkyl(s), an alkanoylamino, an alkylsulfonylamino, an alkyl (said alkyl may be substituted by a group selected from hydroxy, an alkoxy, amino and a carbamoyl which may be substituted by alkyl(s)), carboxy and a carbamoyl which may be substituted by alkyl(s)], (6) phenyl [said phenyl may be substituted by 1 to 3 group(s), being the same or different, and selected

from the group consisting of the following (i) to (vi) : (i) a halogen atom, (ii) an alkoxy, (iii) amino (said amino may be substituted by 1 or 2 group (s), being the same or different, and selected from the group consisting of an alkyl and an alkoxycarbonyl), (iv) an alkoxycarbonyl, (v) carbamoyl, and (vi) morpholinylcarbonyl], (7) a heterocyclic group [said heterocyclic group may be substituted by 1 to 3 group(s), being the same or different, and selected from the group consisting of the following (i) to (v): (i) an alkyl (said alkyl may be substituted by 1 to 3 hydroxy(s)), (ii) hydroxy, (iii) amino, (iv) an alkoxycarbonyl, and(v) carbamoyl], etc. When R^3 to R^8 is an optionally substituted alkyl, said alkyl may have 1 to 3 substituent(s) mentioned above, and when the number of the substituents is 2 or more, each of the substituents may be the same or different.

[0029] When R^3 to R^8 is "a heterocyclic group-substituted alkyl", said heterocyclic group are exemplified by the above-mentioned heterocyclic groups, and preferred are 5- or 6-membered monocyclic heterocyclic groups. Specific examples are pyridyl, pyrimidinyl, pyrazinyl, piperidyl, pyrrolidinyl, morpholinyl, thienyl, furyl, etc.

[0030] When R^3 to R^8 is "an optionally substituted amino", substituents of the amino are exemplified by an alkyl (said alkyl may be substituted by 1 to 3 group(s), being the same or different, and selected from the group consisting of hydroxy, an alkoxy and a heterocyclic group), a cycloalkyl (said cycloalkyl may be substituted by 1 to 3 hydroxy(s)), a heterocyclic group, etc. The said amino may have 1 or 2 substituent(s) mentioned above, and when the number of the substituents is 2 or more, each of the substituents may be the same or different.

[0031] When R^3 to R^8 is "an amino substituted by a heterocyclic group-substituted alkyl" or "an amino substituted by a heterocyclic group", the heterocyclic group are exemplified by the above-mentioned heterocyclic groups. Preferred are 5- or 6-membered monocyclic heterocyclic groups, specific examples are pyridyl, piperidyl, pyrrolidinyl, morpholinyl, etc..

[0032] When R^3 to R^8 is "an optionally substituted alkanoyl", substituents of the alkanoyl are exemplified by hydroxy, an alkoxy, amino (said amino may be substituted by 1 or 2 group(s), being the same or different, and selected from the group consisting of an alkyl and an alkanoyl), an alkoxycarbonyl, etc. The said alkanoyl may have 1 to 3 substituent (s) mentioned above, and when the number of the substituents is 2 or more, each of the substituents may be the same or different.

[0033] When R^3 to R^8 is "an optionally substituted carbamoyl", substituents of the carbamoyl are exemplified by an alkyl, a cycloalkyl, a heterocyclic group, etc. The said carbamoyl may have 1 or 2 substituent(s) mentioned above, and when the number of the substituents is 2, each of the substituents may be the same or different.

[0034] When R^3 to R^8 is "carbamoyl substituted by a heterocyclic group", the heterocyclic group is exemplified by the above-mentioned heterocyclic group, and preferred are 5- or 6-membered monocyclic heterocyclic groups. Specific examples are pyridyl, pyrimidinyl, piperidinyl, etc.

[0035] When R^3 to R^8 is "an optionally substituted cycloalkyl", substituents of the cycloalkyl are exemplified by a halogen atom, an alkyl (said alkyl may be substituted by 1 to 3 group(s) selected from the group consisting of hydroxy, an alkoxy, amino and a carbamoyl which may be substituted by an alkyl), hydroxy, an alkoxy, amino (said amino may be substituted by 1 or 2 group(s), being the same or different, and selected from the group consisting of an alkyl, an alkanoyl, an alkoxycarbonyl and an alkylsulfonyl), carboxy, an alkanoyloxy, an alkoxycarbonyl, carbamoyl (said carbamoyl may be substituted by 1 or 2 group(s), being the same or different, and selected from the group consisting of an alkyl, a cycloalkyl and a heterocyclic group), etc. When R^3 to R^8 is an optionally substituted cycloalkyl, the said cycloalkyl may have 1 to 3 substituent(s) mentioned above, and when the number of the substituents is 2 or more, each of the substituents may be the same or different.

[0036] When R^3 to R^8 is "a cycloalkyl substituted by a heterocyclic group-substituted carbamoyl", the heterocyclic group is exemplified by the above-mentioned heterocyclic groups, and preferred are 5- or 6-membered monocyclic heterocyclic groups. Specific examples are pyridyl, pyrimidinyl, piperidinyl, etc.

[0037] When R^3 to R^8 is "an optionally substituted phenyl", substituents for the phenyl are exemplified by an alkyl, hydroxy, an alkoxy, a halogen atom, amino (said amino may be substituted by 1 or 2 alkyl(s)), etc. The said phenyl may have 1 to 3 substituent(s) mentioned above, and when the number of the substituents is 2 or more, each of the substituents may be the same or different.

[0038] When R^3 to R^8 is "an optionally substituted heterocyclic group", the heterocyclic group is exemplified by the above-mentioned heterocyclic groups, and preferred are 5- or 6-membered monocyclic heterocyclic groups. Specific examples are piperazinyl, piperidyl, pyridyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolidinyl, morpholinyl, oxazolyl, thiazolyl, tetrahydropyranyl, etc. Further, substituents of the heterocyclic group are exemplified by an alkyl (said alkyl may be substituted by 1 to 3 group(s), being the same or different, and selected from the group consisting of phenyl, hydroxy, an alkoxy, amino and a carbamoyl which may be substituted by an alkyl), carboxy, an alkoxycarbonyl, an alkanoyl, an alkylsulfonyl, oxo, etc. The said heterocyclic group may have 1 to 3 substituent(s) mentioned above, and when the number of the substituents is 2 or more, each of the substituents may be the same or different.

[0039] When R^3 to R^8 is "a carbonyl substituted by an optionally substituted cycloalkyl", substituents of the cycloalkyl are exemplified by hydroxy, an alkoxy, amino (said amino may be substituted by 1 or 2 group(s), being the same or different, and selected from the group consisting of an alkyl and an alkanoyl), an alkoxycarbonyl, etc. The said cycloalkyl

may have 1 to 3 substituent(s) mentioned above, and when the number of the substituents is 2 or more, each of the substituents may be the same or different.

[0040] When R^3 to R^8 is "a carbonyl substituted by an optionally substituted phenyl", substituents of the phenyl are exemplified by a halogen atom, hydroxy, an alkoxy, amino (said amino may be substituted by 1 or 2 group(s), being the same or different, selected from the group consisting of an alkyl and an alkanoyl), etc. The said phenyl may have 1 to 3 substituent(s) mentioned above, and when the number of the substituents is 2 or more, each of the substituents may be the same or different.

[0041] When R^3 to R^8 is "a carbonyl substituted by an optionally substituted heterocyclic group", the heterocyclic group is exemplified by the above-mentioned heterocyclic groups, and preferred are 5- or 6-membered monocyclic heterocyclic groups. Specific examples are piperidyl, pyrrolidinyl, pyridyl, pyrimidinyl, morpholinyl, etc. Further, substituents of the heterocyclic group are exemplified by a halogen atom, an alkyl, hydroxy, amino (said amino may be substituted by 1 or 2 alkyl(s)), an alkanoyl, oxo, etc. The said heterocyclic group may have 1 to 3 substituent(s) mentioned above, and when the number of the substituents is 2 or more, each of the substituents may be the same or different.

[0042] R^2 in the compound [Ia] are preferably exemplified by $-NR^3R^4$ and $-OR^5$, and particularly preferably exemplified by $-NR^3R^4$, and further more preferably exemplified by $-NHR^4$.

[0043] When R^2 is $-NHR^4$, preferred examples of R^4 may include an optionally substituted alkyl, an alkenyl, an optionally substituted alkanoyl, an optionally substituted carbamoyl, an optionally substituted cycloalkyl, an optionally substituted phenyl, an optionally substituted heterocyclic group, a carbonyl substituted by an optionally substituted cycloalkyl and a carbonyl substituted by an optionally substituted heterocyclic group. Particularly preferred examples are an optionally substituted alkyl and an optionally substituted cycloalkyl, and more preferred examples are a C_3-C_6 alkyl (said alkyl may be substituted by hydroxy(s)), a C_5-C_7 cycloalkyl (said cycloalkyl may be substituted by a group selected from the group consisting of hydroxy, hydroxymethyl and carbamoyl), etc.

[0044] Although an optical isomer based on an asymmetric carbon can be present in the compounds [I], [Ia] and [Ib] of the present invention, the present invention includes any of these optical isomers as well as mixtures thereof. The compounds [I], [Ia] and [Ib] can be used for a pharmaceutical use, in either a free form or in a form of a pharmaceutically acceptable salt. A pharmaceutically acceptable salt of the compound [I], [Ia] and [Ib] are exemplified by an inorganic acid salt such as a hydrochloride, a sulfate, a phosphate and a hydrobromide, and an organic acid salt such as acetate, fumarate, oxalate, citrate, methanesulfonate, benzenesulfonate, tosylate and maleate, etc. Further, in case of having a substituent such as carboxy, etc., there are mentioned a salt with a base (for example, an alkali metal salt such as a sodium salt, a potassium salt, etc. and an alkaline earth metal such as a calcium salt).

[0045] The compounds [I], [Ia] and [Ib] of the present invention or a salt thereof include an internal salt thereof and a solvate thereof, such as a hydrate, etc.

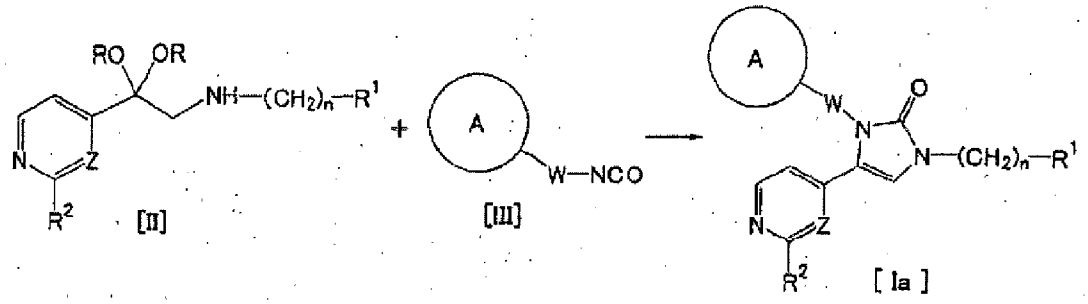
[0046] The compounds [I], [Ia] and [Ib] of the present invention or a pharmaceutically acceptable salt thereof have an excellent p38 MAP kinase inhibitory action and is useful for the prophylaxis and treatment for diseases related to the activation of p38 MAP kinase and the excessive production of inflammatory mediators concerned with p38 MAP kinase such as TNF-α, IL-1, etc. Therefore, the compounds [I], [Ia] and [Ib] of the present invention or a pharmaceutically acceptable salt thereof is expected to be useful for a therapeutic and prophylactic agent for inflammatory diseases, etc. such as arthritis (rheumatoid arthritis, osteoarthritis, infectious arthritis, gouty arthritis, traumatic arthritis, synovitis, periarthritis, etc.), inflammatory bowel disease (ulcerative colitis, Crohn's disease, etc.), inflammatory dermal disease [psoriasis, dermatitis (atopic dermatitis, contact dermatitis urticaria, eczema, etc.), etc.], inflammatory respiratory disease (asthma, bronchitis, pneumonia, pleurisy, pharyngitis, rhinitis, etc.), inflammatory optical disease (conjunctivitis, keratitis, uveitis, etc.), nephritis, hepatitis, systemic inflammatory disease (Behcet's syndrome, systemic lupus erythematosus, etc.), shock (septic shock, endotoxin shock, etc.), cerebrovascular disease (cerebral hemorrhage, cerebral infarction, cerebral edema, etc.), ischemic cardiac diseases (angina pectoris, cardiac infarction, congestive heart failure, etc.), osteoporosis, multiple sclerosis, diabetes, malignant tumor, cachexia, Alzheimer's disease, Parkinson's disease, acquired immunodeficiency syndrome, arterial sclerosis, disseminated intravascular coagulation syndrome, rejection and graft-versus-host diseases by organ transplantation, etc.

[0047] The compounds [I], [Ia] and [Ib] of the present invention or a pharmaceutically acceptable salt thereof can be administered orally or parenterally, and can be used as conventional pharmaceuticals such as tablets, granules, capsules, powder, injections, inhalants, etc. These pharmaceuticals can be prepared according to the conventional methods.

[0048] An administration amount of the compound [I], [Ia] and [Ib] of the present invention or a pharmaceutically acceptable salt thereof depends on an administration method, age, body weight, and condition of the patient, and usually, it is preferably 0.003 to 30 mg/kg, and particularly preferably, 0.01 to 10 mg/kg.

[0049] The compounds [I], [Ia] and [Ib] of the present invention can be prepared suitably by a method selected from the following [Method A] to [Method D], however, it is not limited to these. Production method will be described in detail using the compound [Ia] as follow, however, the compounds [I] and [Ib] can be produced in a similar manner.

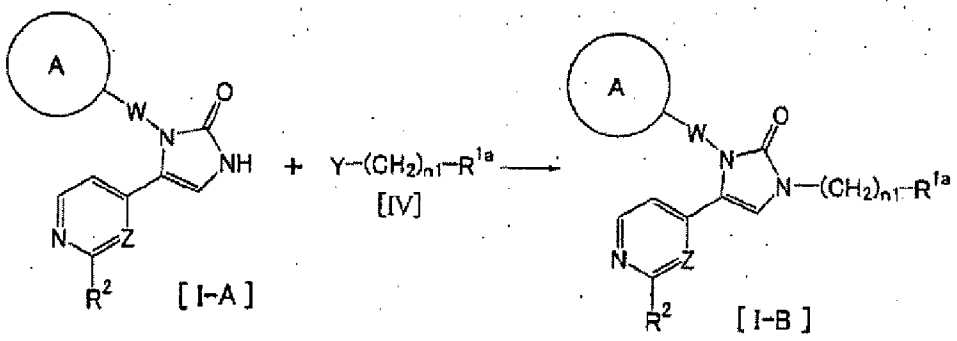
[Method A]



(wherein R is an alkyl, and other symbols have the same meanings as mentioned above.)

[0050] The compound [Ia] of the present invention can be produced by reacting a compound [II] with a compound [III], followed by treating the reaction product with an acid. This reaction can be carried out in a solvent (Journal of Medicinal Chemistry, 9, 858(1966)). As the solvent, there is no limitation as long as it does not affect the reaction, for example, there are mentioned tetrahydrofuran (THF), chloroform, methylene chloride, dioxane, ethyl acetate, ether, toluene, etc. The present reaction proceeds preferably at -20 to 80°C, particularly preferably at 0 to 30°C. Further, as an acid for an acid treatment, there are mentioned, for example, hydrochloric acid, sulfuric acid, phosphoric acid, p-toluenesulfonic acid, methanesulfonic acid, etc. Additionally, as an alkyl of R in the formula [II], there are mentioned, for example, methyl, ethyl, propyl, butyl, etc., and particularly preferred are methyl and ethyl.

[Method B]



(wherein Y is a halogen atom, hydroxy, or dihydroxyboranyl, n1 is 0, 1,2,3 or 4, R^{1a} is hydrogen atom, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted phenyl, or an optionally substituted heterocyclic group (provided that the case where n1 is 0 and R^{1a} is hydrogen atom is excluded.), and other symbols have the same meanings as the above.)

[0051] The compound [I-B] which is categorized in the compound [Ia] can be produced by reacting a compound [I-A], which is a compound [Ia] where n is 0 and R^1 is hydrogen atom, with a compound [IV] for alkylation.

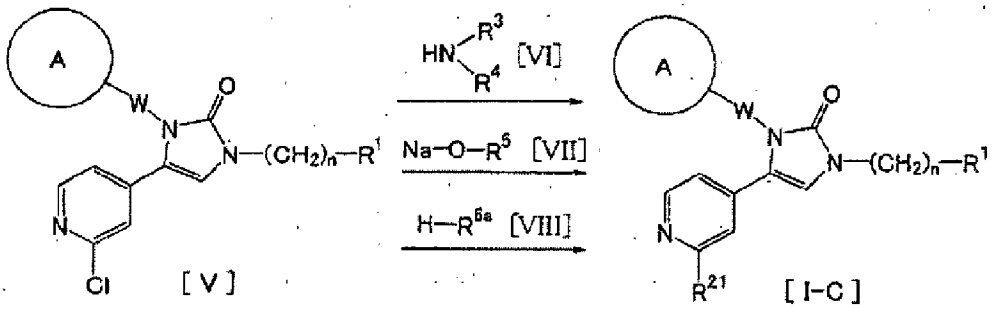
[0052] When Y in the formula [IV] is a halogen atom, this reaction can be carried out in a solvent, in the presence of a base. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, dimethylformamide (DMF), dimethylsulfoxide, 1-methylpyrrolidone, 1,3,-dimethyl-2-imidazolidinone, etc. As the base, there are mentioned, for example, sodium hydride, sodium hydroxide, potassium t-butoxide, butyllithium, lithium diisopropylamide, etc. The reaction proceeds preferably at -20to 100°C, particularly preferably at 0 to 30°C. Further, as the halogen atom at Y, there are mentioned chlorine, bromine and iodine, and bromine and iodine are particularly preferred.

[0053] When Y in the formula [IV] is hydroxy, the reaction can be carried out in a solvent, in the presence of an additive and an activator (Synthesis, 1 (1981)). Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, methylene chloride, THF, dioxane, chloroform, etc. As the additive, there are mentioned, for example, triphenylphosphine, tributylphosphine, trimethylphosphine, etc. As the activator, there are mentioned, for example, diethyl azodicarboxylate, dimethyl azodicarboxylate, 1,1-azobis(N,N-dimethylformamide),

1,1-(azodicarbonyl)dipiperidine, etc. This reaction proceeds preferably at -30 to 100°C, and particularly preferably at 0 to 50°C.

[0054] When Y in the formula [IV] is dihydroxyboranyl, the reaction can be carried out in a solvent, in the presence of a catalyst and a base (Tetrahedron Letters, 39, 2933 (1998)) Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, methylene chloride, chloroform, DMF, etc. As the catalyst, there are mentioned, for example, copper (II) acetate, etc. As the base, there are mentioned, for example, triethylamine, diisopropylethylamine, 4-methylmorpholine, pyridine, etc. This reaction proceeds preferably at -10 to 100°C, and particularly preferably at 20 to 60°C.

[Method C]



(wherein R^{21} is $-NR^3R^4$, $-OR^5$ or $-COR^{6a}$, R^{6a} is an alkoxy, and other symbols have the same meanings as the above.)

[0055] The compound [I-C] which is categorized in the compound [Ia] of the present invention can be produced by reacting a compound [V] with a compound [VI], a compound [VII] or a compound [VIII].

[0056] The reaction between the compound [V] and the compound [VI] can be carried out in a solvent, in the presence of a catalyst, a base and an additive (Journal of Organic Chemistry, 61, 7240(1996)). Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, toluene, xylene, dimethoxyethane, dioxane, etc.

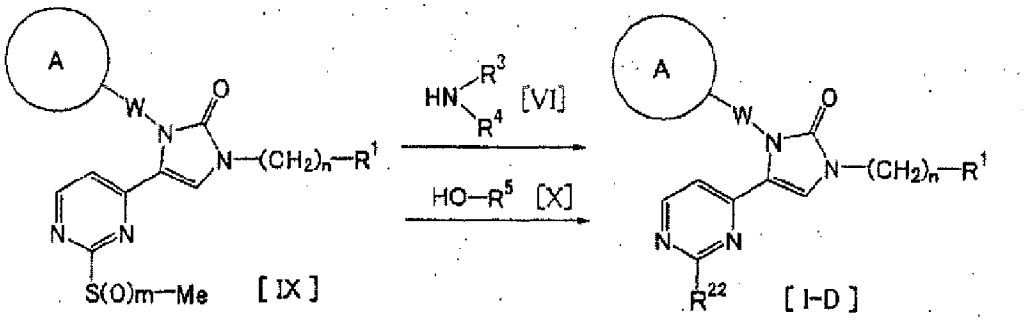
[0057] As the catalyst, there are mentioned, for example, palladium acetate, bis(dibenzylideneacetone)dipalladium, etc. As the base, there are mentioned, for example, sodium t-butoxide, potassium t-butoxide, lithium t-butoxide, triethylamine, etc. As the additive, there are mentioned, for example, 2,2'-bis(diphenylphosphino)-1,1'binaphthyl, etc. The reaction proceeds preferably at 30 to 150°C, and particularly preferably at 60 to 80°C.

[0058] The reaction between the compound [V] and the compound [VII] can be carried out in a solvent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, THF, dioxane, DMF, toluene, methanol, ethanol, etc.

The reaction proceeds preferably at 20 to 150°C, and particularly preferably at 70 to 100°C.

[0059] The reaction between the compound [V] and the compound [VIII] can be carried out in a solvent, in the copresence of carbon monoxide, and in the presence of a catalyst and an additive (Tetrahedron, 55, 393(1999)). Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, toluene, dioxane, DMF, etc. As the catalyst, there are mentioned, for example, palladium acetate, palladium chloride, bis(triphenylphosphine)palladium dichloride, tetrakis(triphenylphosphine)palladium, etc. As the additive, there are mentioned, for example, 1,1'-bis(diphenylphosphino)ferrocene, 1,4-bis(diphenylphosphino)butane, 1,3-bis(diphenylphosphino) propane, triphenylphosphine, etc. The reaction proceeds preferably at 30 to 250°C, and particularly preferably at 80 to 120°C.

[Method D]



(wherein m is 1 or 2, R^{22} is $-NR^3R^4$ or $-OR^5$ and other symbols have the same meanings as the above.)

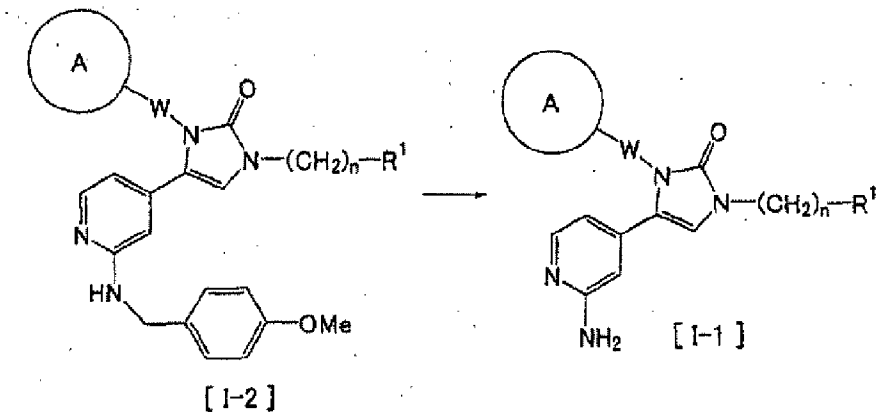
[0060] The compound [I-D] which is categorized in the compound [Ia] of the present invention can be produced by reacting a compound [IX] with a compound [VI] or a compound [X].

[0061] The reaction between the compound [IX] and the compound [VI] can be carried out in a solvent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, dioxane, THF, DMF, dimethylsulfoxide, etc. The reaction proceeds preferably at 0 to 150 °C, and particularly preferably at 50 to 100°C.

[0062] The reaction between the compound [IX] and the compound [X] can be carried out in a solvent, in the presence of a base. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, THF, dioxane, DMF, dimethylsulfoxide, etc. As the base, there are mentioned, for example, sodium hydride, sodium hydroxide, potassium t-butoxide, butyllithium, etc. The reaction proceeds preferably at -30 to 100 °C, and particularly preferably at 0 to 30°C.

[0063] The compound [Ia] produced above can also be derived to other compounds [Ia] by converting a functional group using properly a conventionally known organic chemistry reaction. Such a method for converting a functional group may be suitably selected depending on a kind of a desired functional group. For example, a conversion of a functional group of R^2 in the compound [Ia] can be carried out according to the following (method a) to (method g).

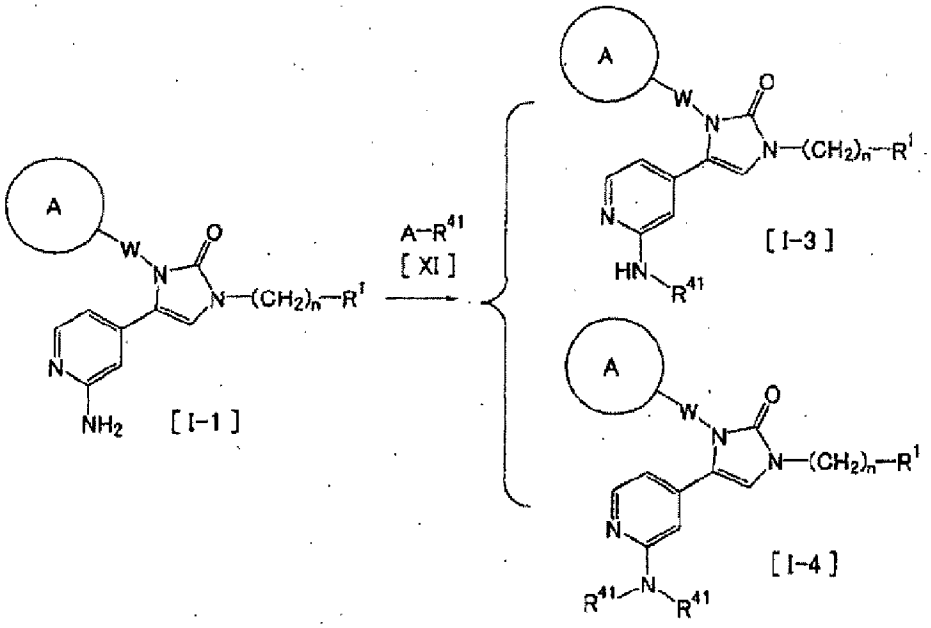
(Method a)



(wherein the symbols have the same meanings as the above.)

[0064] The compound [I-1] can be produced by reacting a compound [I-2] with a hydrogen halide. As the hydrogen halide, there are mentioned hydrogen fluoride, hydrogen chloride, hydrogen bromide, hydrogen iodide, etc., and particularly preferred is hydrogen bromide. This reaction proceeds preferably at 0 to 150°C, particularly preferably at 60 t 80°C.

(Method b)



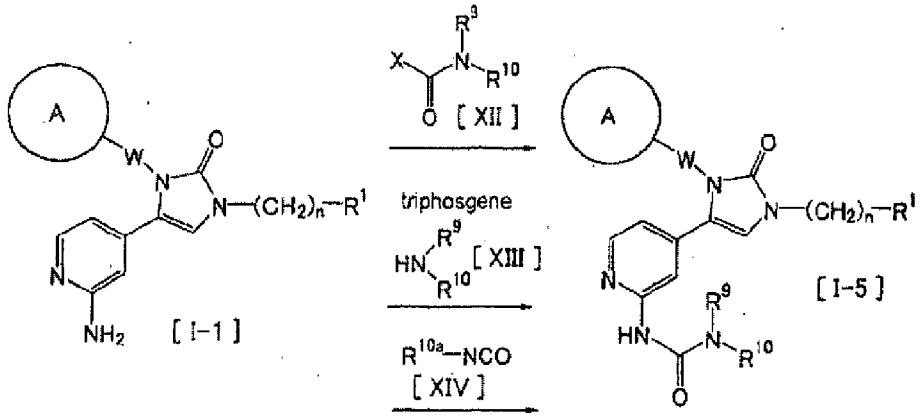
(wherein R^{41} is an alkanoyl which may be substituted, an alkylsulfonyl, carbonyl substituted by a cycloalkyl which may be substituted, carbonyl substituted by a phenyl which may be substituted, or carbonyl substituted by a heterocyclic group which may be substituted. A is a halogen atom or hydroxy. Other symbols have the same meanings as the above.)

[0065] The compound [I-3] and compound [I-4] can be produced by reacting a compound [I-1] with a compound [XI].

[0066] When A in the formula [XI] is a halogen atom, this reaction can be carried out in a solvent in the presence of a base. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, methylene chloride, chloroform, THF, DMF, etc. As the base, there are mentioned, for example, triethylamine, diisopropylethylamine, 4-methylmorpholine, pyridine, etc. The reaction proceeds preferably at -40 to 100°C, particularly preferably at -10 to 30°C. Further, as the halogen atom at X, there are mentioned fluorine, chlorine, bromine, and iodine, and particularly preferred are chlorine and bromine.

[0067] When A in the formula [XI] is hydroxy, this reaction can be carried out in a solvent in the presence of a condensing agent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, methylene chloride, chloroform, THF, DMF, etc. As the condensing agent, there are mentioned, for example, 1,1'-carbonyldiimidazole, 1,3-dicyclohexylcarbodiimide, 1,(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, etc. The reaction proceeds preferably at -40 to 100°C, particularly preferably at -10 to 30°C.

(Method c)



(wherein R^9 and R^{10} are independently hydrogen atom, or an alkyl.
R^{10a} is an alkyl. X is a halogen atom. Other symbols have the same meanings as the above.)

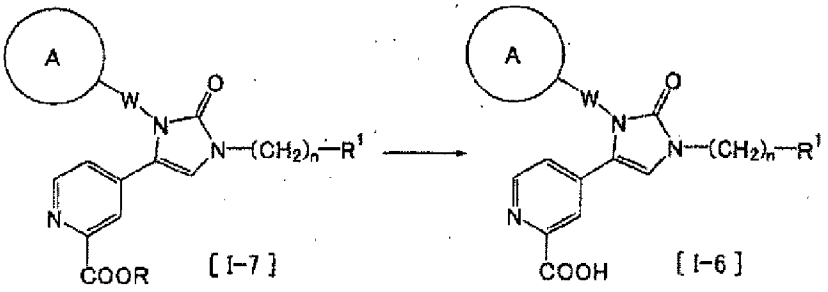
[0068] The compound [I-5] can be produced by reacting a compound [I-1] with a compound [XII], with triphosgene and a compound [XIII], or with a compound [XIV].

[0069] The compound [I-5] can be produced by reacting a compound [I-1] with a compound [XII] in a solvent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, methylene chloride, chloroform, THF, etc. As the halogen atom at X in the formula [XII], fluorine, chlorine, bromine, and iodine are mentioned, and preferred is chlorine. The reaction proceeds preferably at -20 to 100°C and particularly at 10 to 60°C.

[0070] Further, the compound [I-5] can be produced by reacting a compound [I-1] with triphosgene in a solvent, and then, by reacting with a compound [XIII]. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, methylene chloride, chloroform, THF, etc. The reaction proceeds preferably at -20 to 100°C and particularly at 10 to 60°C.

[0071] Still further, a compound [I-5] in which R^9 is a hydrogen atom and R^{10} is an alkyl can be produced by reacting a compound [I-1] with a compound [XIV] in a solvent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, THF, methylene chloride, chloroform, etc. The reaction proceeds preferably at -20 to 100°C and particularly at 10 to 60°C.

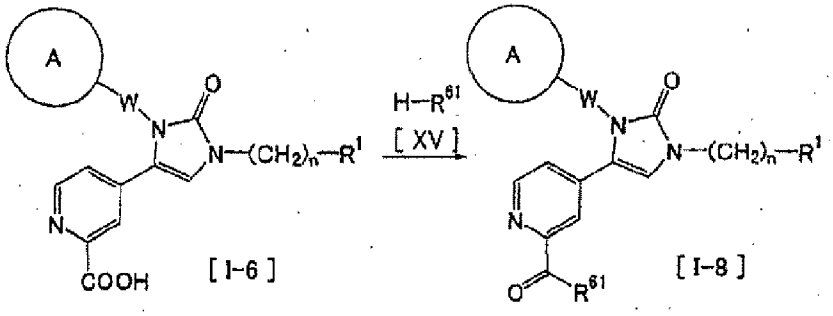
(Method d)



(wherein R is an alkyl, and other symbols have the same meanings as the above.)

[0072] The compound [I-6] can be produced by hydrolyzing a compound [I-7] by a conventional method.

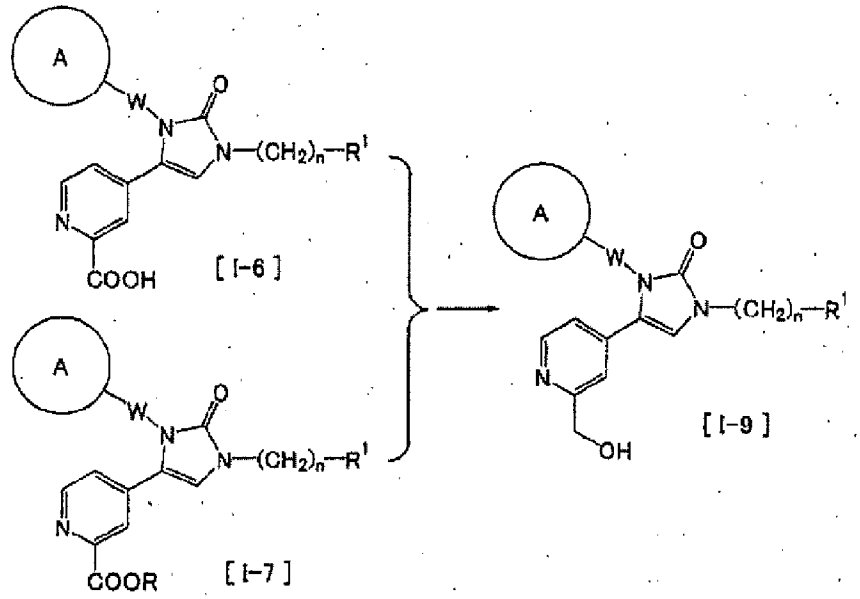
(Method e)



(wherein R^{61} is an amino which may be substituted, and other symbols have the same meanings as the above.)

[0073] The compound [I-8] can be produced by reacting a compound [I-6] with a compound [XV] in a solvent, in the presence of a condensing agent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, methylene chloride, acetonitrile, DMF, THF, etc. As the condensing agent, there are mentioned, for example, 1,1'-carbonyldiimidazole, 1,3-dicyclohexylcarbodiimide, 1,(3-dimethylaminopropyl)-3-ethylcarbodiimide-hydrochloride, etc. The reaction proceeds preferably at -30 to 100°C and particularly at 0 to 70°C.

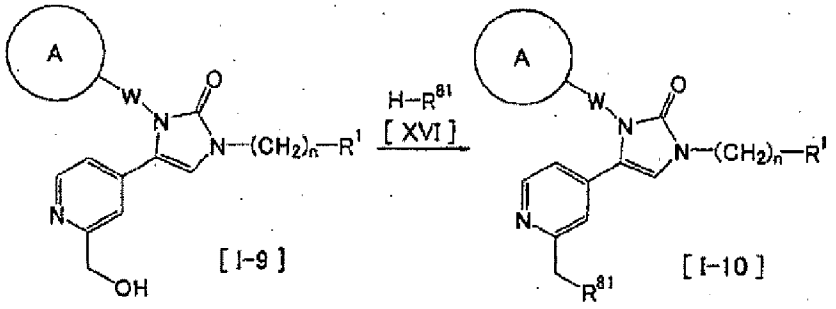
(Method f)



(wherein symbols have the same meanings as the above.)

[0074] The compound [I-9] can be produced by reducing a compound [I-6] or a compound [I-7] in a solvent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, THF, diethyl ether, etc. As the reducing agent, there are mentioned, for example, lithium aluminum hydride, sodium borohydride, lithium borohydride, etc. The reaction proceeds preferably at -20 to 70°C and particularly at 0 to 40°C.

(Method g)



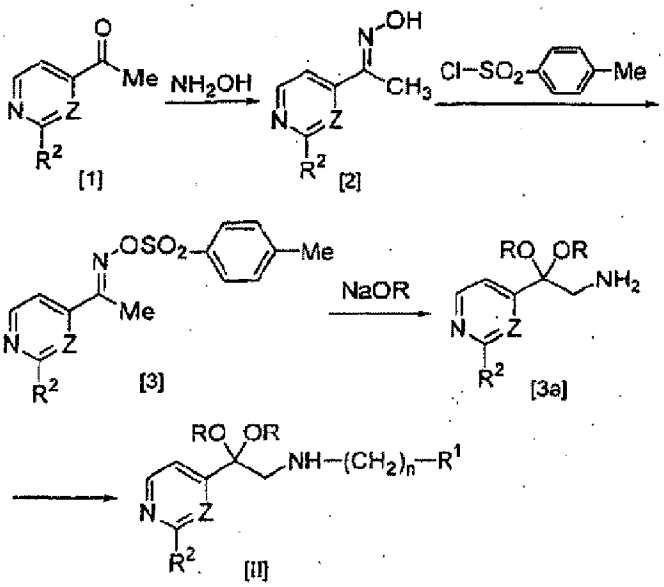
(wherein R^{81} is an optionally substituted amino, and other symbols have the same meanings as the above.)

[0075] The compound [I-10] can be produced by reacting a compound [I-9] with a compound [XVI] in a solvent, in the presence of a base and an activating agent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, methylene chloride, THF, chloroform, toluene, etc. As the base, there are mentioned, for example, triethylamine, diisopropylethylamine, pyridine, etc. As the activating agent, there are mentioned, for example, methanesulfonyl chloride, p-toluenesulfonyl chloride, etc. The reaction proceeds preferably at -10 to 60°C and particularly at 0 to 30°C.

[0076] The compound [Ia] of the present invention obtained according to the above described [Method A] to [Method D] or (Method a) to (Method g) can be optionally converted to a pharmaceutically acceptable salt. Conversion to a pharmaceutically acceptable salt may be carried out by methods known to the person skilled in the art.

[0077] In the following, production methods for starting materials used in the above methods are described.

[0078] The starting material [II] can be produced as follows.



(wherein the symbols have the same meanings as the above.)

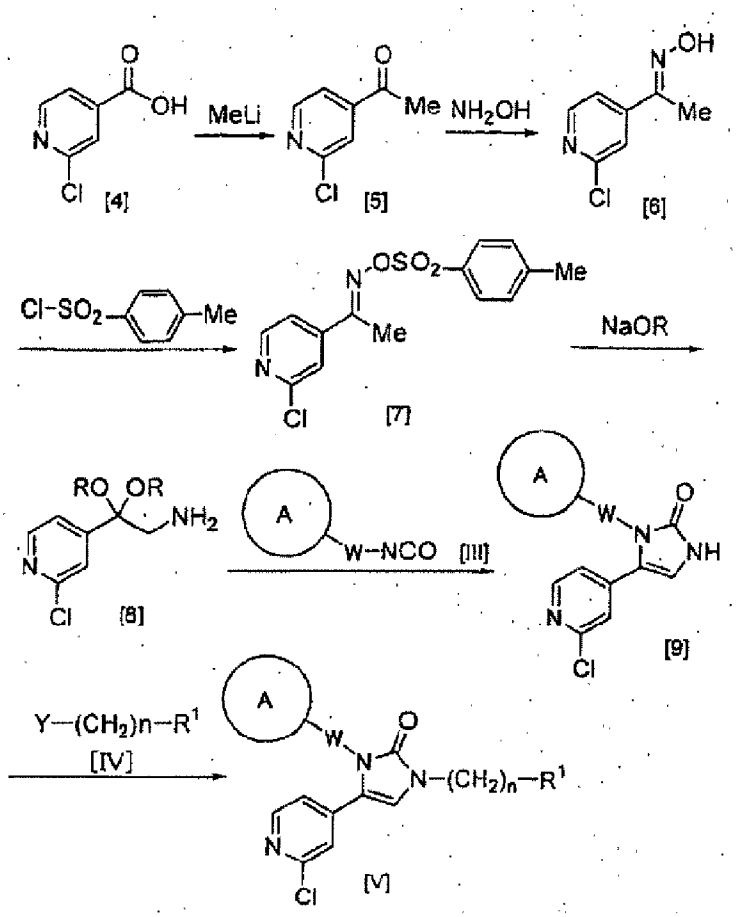
[0079] The reaction for producing the compound [2] from the compound [1] and hydroxylamine can be carried out in a solvent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, ethanol, methanol, etc. The reaction proceeds preferably at 0 to 150°C, and particularly preferably at 60 to 80°C.

[0080] The reaction for producing the compound [3] from the compound [2] and tosyl chloride can be carried out in a solvent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, methylene chloride, chloroform, THF, toluene, etc. As the base, there are mentioned, for example, triethylamine, diisopropylethylamine, pyridine, etc. The reaction proceeds preferably at -20 to 80°C, and particularly preferably at 0 to 30°C.

[0081] The reaction for producing the compound [3a] from the compound [3] can be carried out in a solvent, by reacting the compound [3] with sodium alkoxide, followed by treating the reactant with an acid. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, methanol, ethanol, dioxane, THF, dimethoxyethane, etc. As the acid, there are mentioned, for example, hydrogen chloride, etc. The reaction proceeds preferably at -20 to 60°C, and particularly preferably at 0 to 30°C.

[0082] The reaction for producing the compound [II] from the compound [3a] can be carried out by reacting a corresponding aldehyde using a conventional reductive alkylation (Journal of Organic Chemistry, 61, 3849(1996)).

[0083] A starting material [V] can be produced, for example, as follows.



(wherein the symbols have the same meanings as the above.)

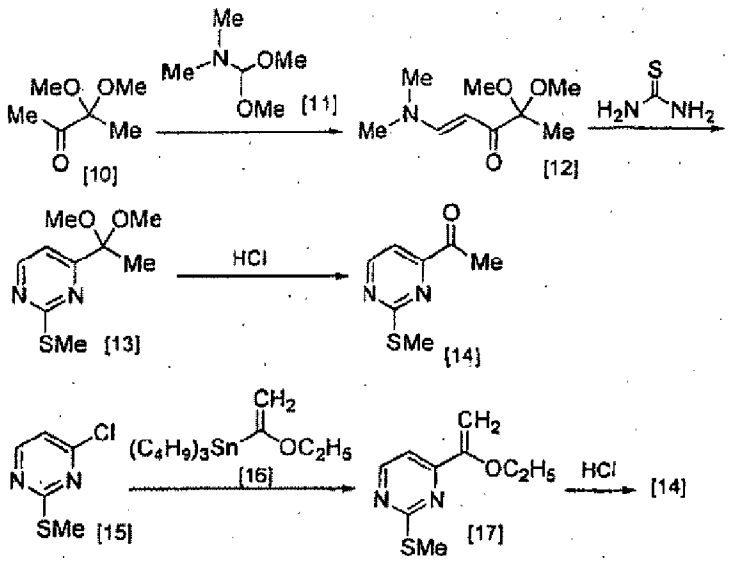
[0084] The reaction for producing the compound [5] from the compound [4] and methyl lithium can be carried out in a solvent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, THF, diethyl ether, dimethoxyethane, etc. The reaction proceeds preferably at -90 to 0°C, and particularly preferably at -60 to -40°C.

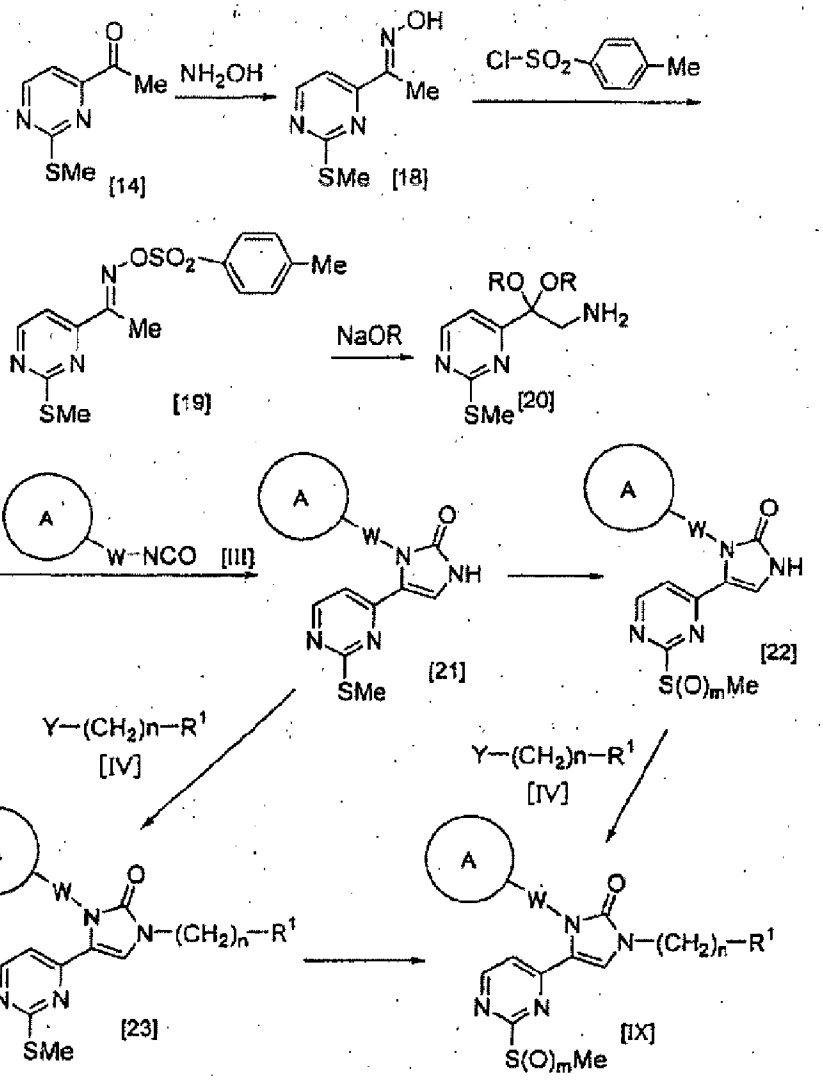
[0085] The method for producing the compound [8] from the compound [5] via the compound [6] and the compound [7] can be carried out in a similar manner to the above-mentioned method for producing the compound [II] from the compound [1] via the compound [2] and the compound [3].

[0086] The reaction for producing the compound [9] from the compound [8] and the compound [III] can be carried out in a similar manner to the above-mentioned [Method A].

[0087] The reaction for producing the compound [V] from the compound [9] and the compound [IV] can be carried out in a similar manner to the above-mentioned [Method B].

[0088] A starting material [IX] can be produced, for example, as follows.


Me
Me
N
OMe
OMe
[11]
MeO
OMe
Me
Me
O
[10]
Me
N
Me
MeO
OMe
Me
O
[12]
S
H2N
NH2
MeO
OMe
Me
N
N
SMe
[13]
HCl
O
Me
N
N
SMe
[14]
Cl
N
N
SMe
[15]
CH2
(C4H9)3Sn
OC2H5
[16]
CH2
OC2H5
N
N
SMe
[17]
HCl
[14]



(wherein m is 1 or 2, and other symbols have the same meanings as the above.)

[0089] The reaction for producing the compound [12] from the compound [10] and the compound [11] can be carried out in a solvent or without solvent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, toluene, xylene, dioxane, etc. The reaction proceeds preferably at 50 to 150°C, and particularly preferably at 80 to 120°C.

[0090] The reaction for producing the compound [13] from the compound [12] can be carried out by reacting the compound [12] with thiourea in a solvent, in the presence of a base, and then, by reacting an alkylating agent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, methanol, THF, dioxane, etc. As the base, there are mentioned, for example, sodium methoxide, sodium hydroxide, potassium t-butoxide, etc. As the alkylating agent, there are mentioned, for example, methyl iodide, dimethyl sulfate, etc. The reaction proceeds preferably at 0 to 100°C, and particularly preferably at 30 to 70°C.

[0091] The reaction for producing the compound [14] from the compound [13] can be carried out in a solvent, in the presence of an acid. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, water, acetone, THF, dioxane, etc. As the acid, there are mentioned, for example, hydrochloric acid, sulfuric acid, phosphoric acid, p-toluenesulfonic acid, etc. The reaction proceeds preferably at -10 to 80°C, and particularly preferably at 0 to 30°C.

[0092] The compound [14] can be also produced from the compound [15] via the compound [17].

[0093] The reaction for producing the compound [17] from the compound [15] and the compound [16] can be carried out in a solvent, in the presence of a catalyst. Any solvent can be used as long as it does not affect the reaction, and

there are mentioned, for example, DMF, toluene, xylene, etc. As the catalyst, there are mentioned, for example, bis (triphenylphosphine)palladium dichloride, tetrakis(triphenylphosphine)palladium, etc. The reaction proceeds preferably at 50 to 150°C, and particularly preferably at 70 to 90°C.

[0094] The reaction for producing the compound [14] from the compound [17] can be carried out in a similar manner to the above-mentioned method for producing the compound [14] from the compound [13].

[0095] The reaction for producing the compound [20] from the compound [14] via the compound [18] and the compound [19] can be carried out in a similar manner to the above-mentioned method for producing the compound [II] from the compound [1] via the compound [2] and the compound [3].

[0096] The reaction for producing the compound [21] from the compound [20] and the compound [III] can be carried out in a similar manner to the above-mentioned [Method A].

[0097] The reaction for producing the compound [22] from the compound [21] can be carried out in a solvent, using an oxidizing agent. Any solvent can be used as long as it does not affect the reaction, and there are mentioned, for example, water, methanol, THF, dioxane, chloroform, methylene chloride, etc. As the oxidizing agent, there are mentioned, for example, Oxon (trade name, manufactured by DuPont Co. Ltd.), 3-chloroperoxybenzoic acid, hydrogen peroxide, etc. The reaction proceeds preferably at -20 to 60°C, and particularly preferably at -10 to 30°C.

[0098] The reaction for producing the compound [IX] from the compound [22] and the compound [IV] can be carried out in a similar manner to the above-mentioned [Method B].

[0099] The compound [IX] can be also produced from the compound [21] via the compound [23].

[0100] The reaction for producing the compound [23] from the compound [21] and the compound [IV] can be carried out in a similar manner to the above-mentioned [Method B].

[0101] The reaction for producing the compound [IX] from the compound [23] can be carried out in a similar manner to the reaction for producing the compound [22] from the compound [21].

[0102] Incidentally, in the above production methods, it is possible to optionally protect or deprotect a functional group. As the protecting group for the functional group, those used in a field of conventional organic synthetic chemistry can be used, examples of which include those described in "Protective Groups in Organic Synthesis" by T. W. Greene, P. M. G. Wuts, (published by John Wiley and Sons, 1991). For conditions for introducing protecting groups or condition for de-protection, the method described in the above reference can be mentioned.

[0103] Further, each compound and each intermediate produced in the above production methods can be purified by means of a conventional method, for example, column chromatography, recrystallization, etc. As a solvent for recrystallization, there are mentioned, for example, an alcohol solvent such as methanol, ethanol, 2-propanol, etc., an ether solvent such as diethyl ether, etc., an ester solvent such as ethyl acetate, etc., an aromatic solvent such as toluene, etc., a ketone solvent such as acetone, etc., a hydrocarbon solvent such as hexane, etc., water, etc., and a mixed solvent thereof. Further, the compounds [I], [Ia] and [Ib] of the present invention can be converted to a pharmaceutically acceptable salt according to the conventional method, and recrystallization can be carried out afterwards.

Examples

[0104] Hereinbelow, the present invention will be explained in more detail with reference to the following Examples, which should not be construed as limiting the scope of the present invention.

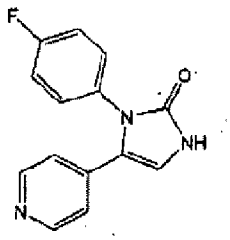
[0105] Each of the following symbols used in the present specification represents the meaning as described below.

Me :	methyl
Et :	ethyl
THF:	tetrahydrofuran
DMF:	N,N-dimethylformamide
t- :	tert-

Example 1

1-(4-Fluorophenyl)-5-(pyridin-4-yl)-4-imidazolin-2-one

[0106]

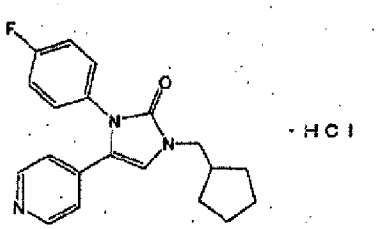


[0107] A solution of 3.00 g of 2,2-diethoxy-2-pyridin-4-ylethylamine (a compound obtained in Reference Example 2) dissolved in 30 ml of THF was cooled by water, and 1.97 g of 4-fluorophenylisocyanate was added by dropwise. After addition, the reaction mixture was concentrated under reduced pressure, and then, 30 ml of conc. hydrochloric acid was added to the obtained residue, and the mixture was stirred at room temperature overnight. To 180 ml of an ice cold aqueous 2N NaOH solution was added the reaction mixture for neutralization, and precipitated crystals were collected by filtration. They were washed with water and ether, air-dried at 60°C, to give 3.10 g of the title compound as colorless crystals. Melting point: 261°C (decomposed)

Example 2

1-Cyclopentylmethyl-3-(4-fluorophenyl)-4-(pyridin-4-yl)-4-imidazolin-2-one · hydrochloride

[0108]

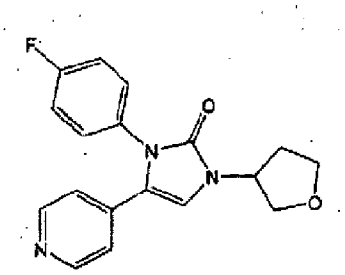


[0109] 128 mg of 1-(4-Fluorophenyl)-5-(pyridin-4-yl)-4-imidazolin-2-one (the compound of Example 1), 61 μl of cyclopentylmethanol, 197 mg of triphenylphosphine and 295 μl of diethyl azodicarboxylate were dissolved in 2.5 ml of methylene chloride, and the mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform : ethyl acetate = 19 : 1). The obtained compound was treated with hydrochloric acid, to give 75 mg of the title compound as powder.

Example 3

1-(Oxolan-3-yl)-3-(4-fluorophenyl)-4-(pyridin-4-yl)-4-imidazolin-2-one

[0110]

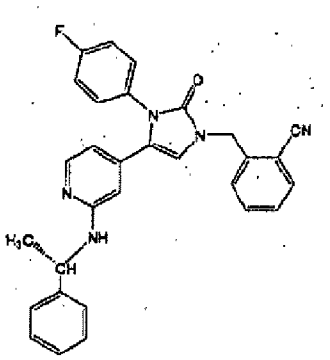


[0111] The title compound was given by treating the corresponding starting material in a similar manner to that in Example 2. Melting point : 132-134°C

Example 4

1-(2-Cyanobenzyl)-3-(4-fluorophenyl)-4-[(2-(1-(S)-phenylethylamino)pyridin-4-yl)]-4-imidazolin-2-one

[0112]

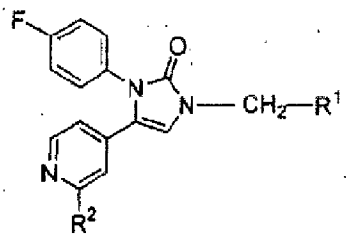


[0113] 50 mg of 4-(2-Chloropyridin-4-yl)-3-(4-fluorophenyl)-1-(2-cyanobenzy 1)-4-imidazolin-2-one (a compound of Reference Example 1 (6)), 79 μl of (S)-(-)-α-methylbenzylamine, 5.5 mg of palladium acetate, 15 mg of 2,2'-bis(diphenylphsophino)-1,1'-binaphthyl and 17 mg of sodium t-butoxide were suspended in 1 ml of toluene, and the mixture was stirred at 70°C for 18 hours, under nitrogen flow. The reaction mixture was diluted by ethyl acetate, and insoluble matter was removed by filtration through Celite. To the filtrate was added 6N hydrochloric acid, and after separation, an aqueous layer was made alkaline with aqueous sodium bicarbonate solution. The mixture was extracted with chloroform, washed with saturated brine, and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 2), to give 38 mg of the title compound as colorless powder.

Examples 5 - 12

[0114] Compounds in Table 1 were obtained by treating the corresponding starting materials in a similar manner to that in Example 4.

Table 1



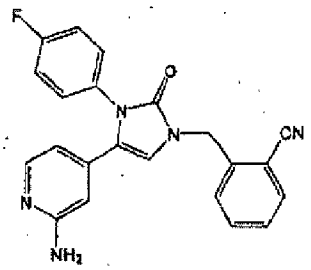
Example	R^1	R^2	Physical properties, etc.
5	2-Cyanophenyl	4-Methoxybenzylamino	Melting point 167°C
6	2-Cyanophenyl	2-Thienylmethylamino	Melting point 171°C
7	2-Cyanophenyl	(S)-1-t-Butoxycarbonylethylamino	Melting point 191-193°C
8	2-Cyanophenyl	Isopropylamino	Melting point 170-171°C
9	2-Cyanophenyl	Allylamino	Melting point 163°C
10**	2-Methoxyphenyl	2-Pyridylmethylamino	Melting point 248-250°C
11	2-Fluorophenyl	2-(2-Pyridyl)ethylamino	Melting point 132-134°C
12**	2-Trifluoromethylphenyl	2-(2-Pyridyl)ethylamino	Powder

**:Dihydrochloride

Example 13

4-(2-Aminopyridin-4-yl)-1-(2-cyanobenzyl)-3-(4-fluorophenyl)-4-imidazolin-2-one

[0115]

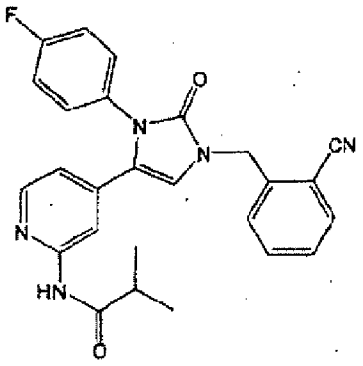


To 1.5 g of 1-(2-cyanobenzyl)-3-(4-fluorophenyl)-4-[2-(4-methoxybenzylamino)pyridin-4-yl]-4-imidazolin-2-one (Compound of Example 5) was added 3 ml of 25% hydrogen bromide-acetic acid solution, and the mixture was stirred at 70°C for one hour. The reaction mixture was concentrated under reduced pressure, and the residue was made alkali with an aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate, washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (chloroform:methanol=20:1) to give 572 mg of the title compound as colorless crystal. Melting point :182-183°C.

Example 14

4-(2-N-Isobutyroylaminopyridin-4-yl)-1-(2-cyanobenzyl)-3-(4-fluorophenyl)-4-imidazolin-2-one

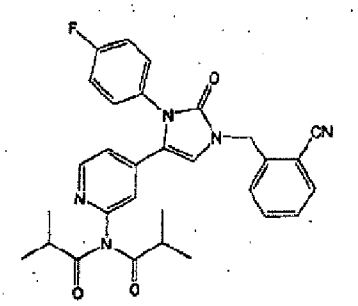
[0116]



Example 15

4-(2-N,N-Diisobutyroylaminopyridin-4-yl)-1-(2-cyanobenzyl)-3-(4-fluorophenyl)-4-imidazolin-2-one

[0117]

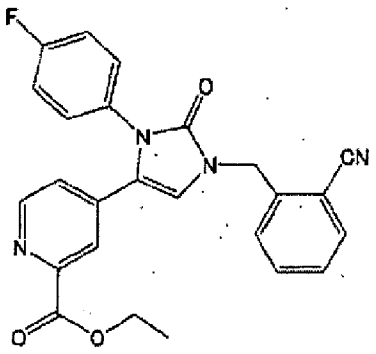


A suspension of 50 mg of 4-(2-aminopyridin-4-yl)-1-(2-cyanobenzyl)-3-(4-fluorophenyl)-4-imidazolin-2-one (Compound of Example 13) and 20 µl of isobutyroyl chloride in methylene chloride was ice-cooled, and after adding 54 µl of triethylamine by dropwise, and the mixture was stirred at room temperature for 3 hours. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate, washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (chloroform: acetone=20:1) to give 22 mg of the title compound (Example 14) as colorless crystal and 10 mg of the title compound (Example 15) as colorless crystal, respectively. Melting point:196°C (Example 14), 185-187°C (Example 15).

Example 16

4-(2-Ethoxycarbonylpyridin-4-yl)-1-(2-cyanobenzyl)-3-(4-fluorophenyl)-4-imidazolin-2-one

[0118]

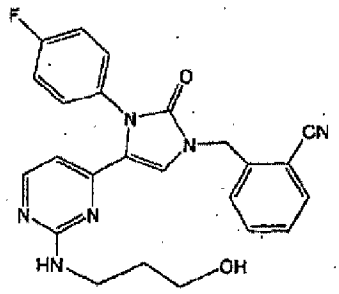


In 20 ml of ethanol were suspended 1 g of 4-(2-chloropyridin-4-yl)-3-(4-fluorophenyl)-1-(2-cyanobenzyl)-4-imidazolin-2-one [Compound of Reference example 1(6)], 55 mg of palladium acetate, 137 mg of 1,1'-bis(diphenylphosphino)-ferrocene and 608 mg of sodium acetate, the mixture was stirred under carbon monoxide atmosphere at 80°C for 12 hours. The reaction mixture was concentrated under reduced pressure, the residue was suspended in ethyl acetate, treated with activated charcoal and then filtered. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:2) to give 887 mg of the title compound as colorless crystal. Melting point:164°C.

Example 17

1-(2-Cyanobenzyl)-3-(4-fluorophenyl)-4-[2-(3-hydroxypropylamino)pyrimidin-4-yl]-4-imidazolin-2-one

[0119]

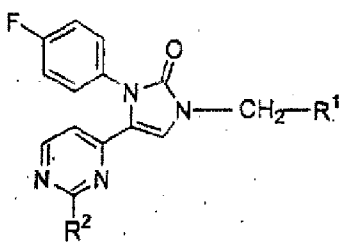


[0120] A mixture of 70 mg of 1-(2-cyanobenzyl)-3-(4-fluorophenyl)-4-(2-methylsulfinylpyrimidin-4-yl)-4-imidazolin-2-one (Compound of Reference example 6 (2) or Reference example 7(2)), 60.6 mg of 3-aminopropanol and 2 ml of dioxane was stirred at 80°C for 5 hours. The reaction mixture was concentrated and then purified by silica gel column chromatography (chloroform: methanol=19:1) and crystallized from ether to give 44.6 mg of the title compound. Melting point: 166-167°C.

Examples 18 to 24

[0121] The corresponding starting materials were treated in the same manner as in Example 17 to give Compounds in Table 2.

Table 2

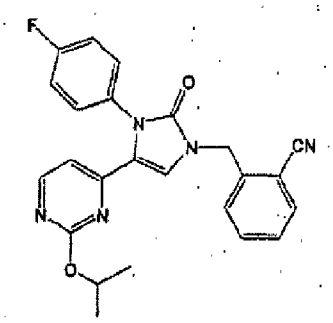


Example	R^1	R^2	Physical properties, etc.
18	2-Cyanophenyl	2-Furylmethylamino	Melting point 174-175°C
19	2-Cyanophenyl	3-Methoxypropylamino	Melting point 168-169°C
20	2-Cyanophenyl	Isobutylamino	Melting point 145-146°C
21	2-Cyanophenyl	Allylamino	Melting point 189-190°C
22	2-Cyanophenyl	4-Hydroxybutylamino	Melting point 166-167°C
23	2-Methoxyphenyl	Isopropylamino	Melting point 171-172°C
24	2-Fluorophenyl	Isopropylamino	Melting point 120-122°C

Example 25

1-(2-Cyanobenzyl)-3-(4-fluorophenyl)-4-(2-isopropoxypyrimidin-4-yl)-4-imidazolin-2-one

[0122]

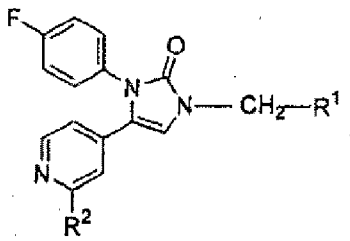


[0123] In 5 ml of isopropanol was suspended 100 mg of 1-(2-cyanobenzyl)-3-(4-fluorophenyl)-4-(2-methylsulfinylpyrimidin-4-yl)-4-imidazolin-2-one (Compound of Reference example 6 (2) or Reference example 7(2)), 26.3 mg of sodium hydride was added to the mixture and the resulting mixture was stirred at room temperature for 5 hours. To the reaction mixture were successively added an aqueous citric acid solution and an aqueous sodium bicarbonate solution, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed, dried and concentrated, and the residue was purified by silica gel column chromatography (chloroform:methanol=30:1) to give 68 mg of the title compound as powder.

Examples 26 to 79

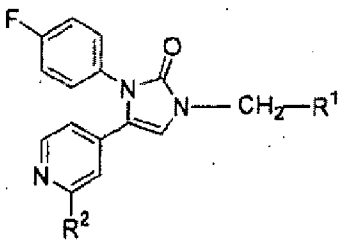
[0124] The compound of Reference example 1(5) and the corresponding starting materials were subjected to N-alkylation in the same manner as in Example 2 or Reference example 1(6), and then, subjected to amination in the same manner as in Example 4 to give the compounds shown in Tables 3 to 6.

Table 3



Example	R^1	R^2	MS ($[M+H]^+$)
26	2-Cyanophenyl	Benzylamino	476
27	2-Cyanophenyl	Cyclopropylamino	426
28	2-Cyanophenyl	2-Furylmethylamino	466
29	2-Cyanophenyl	2-Pyridylmethylamino	477
30	2-Cyanophenyl	Cyclopentylamino	454
31	2-Cyanophenyl	4-Chlorobenzylamino	510
32	2-Cyanophenyl	2-Methoxybenzylamino	506
33	2-Cyanophenyl	3-Methoxybenzylamino	506
34	2-Cyanophenyl	3-Pyridylmethylamino	477
35	2-Cyanophenyl	2-Methylpyridin-4-ylmethyl amino	491
36	2-Cyanophenyl	2-(2-Pyridyl)-ethylamino	491
37	2-Cyanophenyl	(4-Methyl-1-piperazinyl)-amino	484
38	2-Cyanophenyl	3-Methoxypropylamino	458
39	2-Cyanophenyl	3-Propoxypropylamino	486

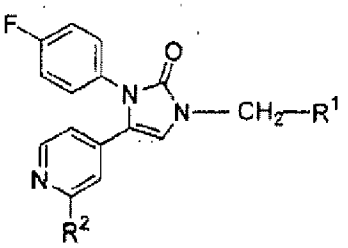
Table 4



Example	R^1	R^2	MS ([M+H]$^+$)
40	2-Cyanophenyl	Cyclopropylmethylamino	440
41	2-Cyanophenyl	3-Isopropoxypropylamino	486
42	2-Fluorophenyl	2-Pyridylmethylamino	470
43**	2-Trifluoro-methylphenyl	2-Pyridylmethylamino	520
44	2-Cyanophenyl	Isobutylamino	442
45	2-Cyanophenyl	2-Ethoxyethylamino	458
46	2-Trifluoro-methylphenyl	Isopropylamino	471
47	2-Fluorophenyl	Isopropylamino	421
48	2-Methoxyphenyl	Isopropylamino	433
49	2-Fluorophenyl	Isobutylamino	435
50	2-Methoxyphenyl	Isobutylamino	447
51	2-Cyanophenyl	t-Butylamino	442
52	2-Cyanophenyl	4-Tetrahydropyranylamino	470
53	2-Cyanophenyl	(S)-1-(2-Pyridyl)ethyl-amino	491

**: Dihydrochloride

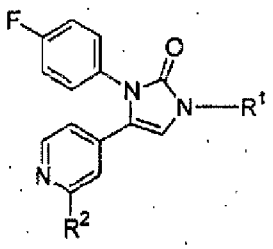
Table 5



Example	R^1	R^2	MS ([M+H]$^+$)
54	2-Fluorophenyl	trans-4-Hydroxycyclohexylamino	477
55	4-Methoxyphenyl	Isopropylamino	433
56	2-Cyanophenyl	trans-4-Hydroxycyclohexylamino	484
57	4-Methoxyphenyl	(S)-1-(2-Pyridyl)ethylamino	495
58	2-Fluorophenyl	4-Methoxybenzylamino	499
59	cis-4-Methoxymethoxycyclohexyl	Isobutylamino	483
60	cis-4-Methoxymethoxycyclohexyl	trans-4-Hydroxycyclohexylamino	524
61	cis-4-Methoxymethoxycyclohexyl	Isopropylamino	469
62	2-Fluorophenyl	(1-Methyl-4-piperidyl)amino	476
63	2-Fluorophenyl	(1-t-Butoxycarbonyl-4-piperidyl)amino	562
64	2-Cyanophenyl	(1-Methyl-4-piperidyl)amino	483
65*	Cyclopentyl	Isopropylamino	395
66	Cyclopentyl	trans-4-Hydroxycyclohexylamino	451
67*	4-Tetrahydropyranyl	Isopropylamino	411

*:Monohydrochloride ; **:Dihydrochloride

Table 6

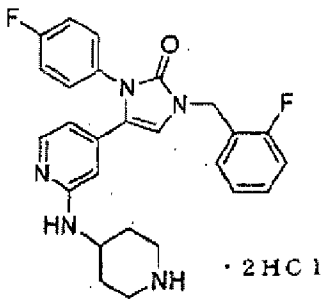


Example	R^1	R^2	MS ($[M+H]^+$)
68*	4-Tetrahydropyranyl	trans-4-Hydroxycyclohexylamino	467
69	2-Methoxyethyl	trans-4-Hydroxycyclohexylamino	427
70	Methoxymethyl	trans-4-Hydroxycyclohexylamino	413
71	Methoxymethyl	Isopropylamino	357
72	Methyl	trans-4-Hydroxycyclohexylamino	383
73*	Ethyl	trans-4-Hydroxycyclohexylamino	397
74	Isopropyl	trans-4-Hydroxycyclohexylamino	411
75**	Isopropyl	trans-4-Aminocyclohexylamino	410
76*	Isopropyl	trans-4-Acetylamino-cyclohexylamino	452
77*	N-Isopropyl-carbamoylmethyl	Isopropylamino	412
78**	Isopropyl	trans-4-Dimethylamino-cyclohexylamino	438
79**	Isopropyl	trans-4-Carbamoylmethylamino-cyclohexylamino	467

*:Monohydrochloride ; **:Dihydrochloride

Example 80

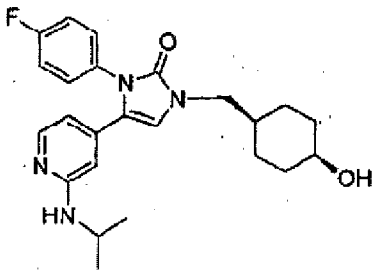
[0125]



[0126] To 146 mg of the compound in Example 63 were added 0.2 ml of ethyl acetate and 1. 7 ml of a 4N hydrogen chloride-ethyl acetate solution, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, and ethyl acetate was added to the residue and powder was collected by filtration to give 128 mg of the title dompound.
MS 462([M+H]+)

Example 81

[0127]

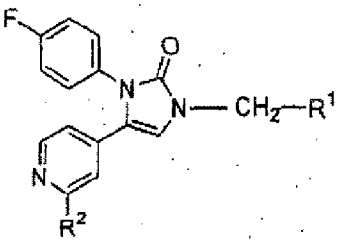


[0128] To 2 ml of methanol was dissolved 148 mg of the compound in Example 61, 1 ml of conc. hydrochloric acid was added to the mixture and the resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was neutralized with a 4N aqueous NaOH solution and extracted with chloroform. After drying and concentration, diethyl ether and diisopropyl ether were added to the residue and the resulting powder was collected by filtration to give 58 mg of the title compound.
MS 425([M+H]+)

Examples 82 to 107

[0129] The compounds of Examples 26 to 79 or the corresponding starting materials obtained in the similar method were treated in the same manner as in Example 80 or Example 81 to give the compounds shown in Tables 7 to 9.

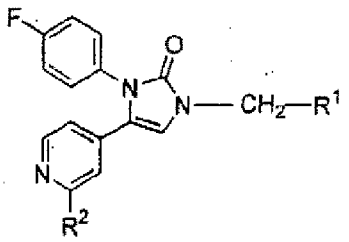
Table 7



Example	R^1	R^2	MS ($[M+H]^+$)
82**	4-Piperidyl	Isopropylamino	410
83**	2-Cyanophenyl	4-Piperidylamino	469
84	cis-4-Hydroxy-cyclohexyl	Isobutylamino	439
85**	cis-4-Aminocyclo-hexyl	Isopropylamino	424
86**	cis-4-Aminocyclo-hexyl	trans-4-Hydroxycyclo-hexylamino	480
87	cis-4-Hydroxy-cyclohexyl	trans-4-Hydroxycyclo-hexylamino	481
88	cis-4-Hydroxy-cyclohexyl	(1-Methyl-4-Piperidyl) amino	480
89	trans-4-Amino-cyclohexyl	trans-4-Hydroxycyclo-hexylamino	480
90**	4-Piperidyl	Isobutylamino	424
91**	4-Piperidyl	trans-4-Hydroxycyclo-hexylamino	466
92**	trans-4-Amino-cyclohexyl	Isobutylamino	438
93**	cis-4-Aminocyclo-hexyl	Isobutylamino	438
94***	cis-4-Aminocyclo-hexyl	4-Piperidylamino	465

:Dihydrochloride ; *:Trihydrochloride

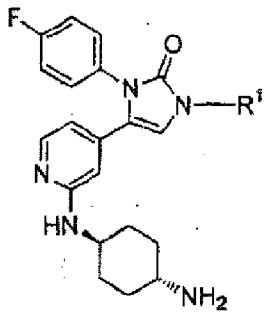
Table 8



Example	R^1	R^2	MS ($[M+H]^+$)
95**	cis-4-Hydroxy-cyclohexyl	4-Piperidylamino	466
96***	trans-4-Amino-cyclohexyl	4-Piperidylamino	465
97**	trans-4-Amino-cyclohexyl	Isopropylamino	424
98**	2-Fluorophenyl	trans-4-Aminocyclohexyl amino	476
99**	2-Cyanophenyl	trans-4-Aminocyclohexyl amino	483
100*	trans-4-Hydroxy-cyclohexyl	Isopropylamino	425
101*	trans-4-Hydroxy-cyclohexyl	Isobutylamino	439
102*	trans-4-Hydroxy-cyclohexyl	trans-4-Hydroxycyclo-hexylamino	481
103	1-Hydroxycyclo-propyl	Isopropylamino	383
104*	1-Hydroxycyclo-propyl	trans-4-Hydroxycyclo-hexylamino	439

*:Monohydrochloride;**:Dihydrochloride;***:Trihydrochloride

Table 9



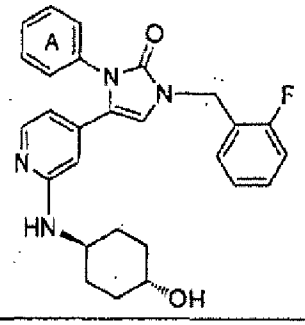
Example	R^1	MS ([M+H]$^+$)
105	Methoxymethyl	412
106**	2-Methoxyethyl	426
107**	Ethyl	396

**:Dihydrochloride

Examples 108 to 126

[0130] The compound of Reference example 8 and a corresponding isocyanate were reacted in the same manner as in Example 1 to carry out cyclization, and the corresponding amine was reacted in the same manner as in Example 4 to give the compounds shown in Tables 10 and 11.

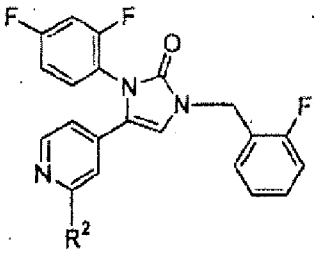
Table 10



Example	Ring A	MS ([M+H]$^+$)
108	Phenyl	459
109*	2-Fluorophenyl	477
110*	3-Fluorophenyl	477
111*	3,4-Difluorophenyl	495
112*	2,4-Difluorophenyl	495
113*	4-Chlorophenyl	493
114*	4-Methylphenyl	473
115*	4-Methoxyphenyl	489
116*	3-Methoxyphenyl	489
117*	4-Fluorobenzyl	491
118*	3-Trifluoromethylphenyl	527
119*	3-Chlorophenyl	493
120*	3-Methylphenyl	473
121*	4-Fluoro-3-Methoxyphenyl	507
122*	3-Hydroxyphenyl	475
123*	2-Thienyl	465

*:Monohydrochloride

Table 11

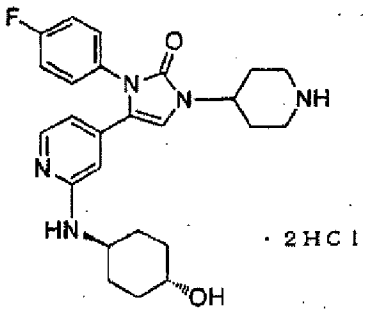


Example	R^2	MS ([M+H]$^+$)
124*	Isopropylamino	439
125*	Isobutylamino	453
126**	(1-Methyl-4-piperidyl)amino	494

*:Monohydrochloride ; **:Dihydrochloride

Example 127

[0131]

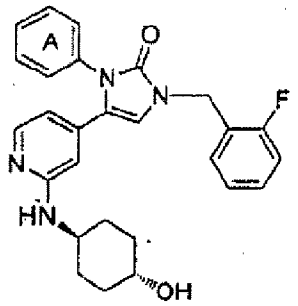


[0132] The compoud of Reference example 9 was subjected to amination in the same manner as in Example 4, and then, treated in the same manner as in Example 80 to give the title compound.
MS 452([M+H]$^+$)

Examples 128 to 141

[0133] The compound of Reference example 8 or Reference example 10 and a corresponding starting compound were subjected to amination in the same manner as in Example 4, and then, the resulting compound was treated with a corresponding isocyanate in the same manner as in Example 1 to carry out cyclization to give the compounds shown in Tables 12 and Table 13.

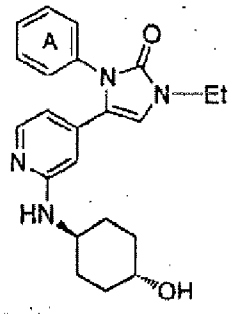
Table 12



Example	Ring A	MS ([M+H]$^+$)
128*	3-Amino-4-fluorophenyl	492
129*	3-Aminophenyl	474
130*	3-hydroxymethylphenyl	489
131*	2-Aminophenyl	474
132*	2-Nitrophenyl	504
133*	4-Fluoro-2-nitrophenyl	522
134*	2-Cyanophenyl	484
135*	3,5-Difluorophenyl	495
136*	2-Carbamoylphenyl	502

*:Monohydrochloride

Table 13



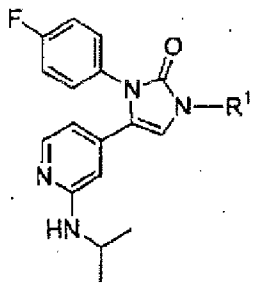
Example	Ring A	MS ([M+H]$^+$)
137*	3-Chlorophenyl	413
138*	3-Methylphenyl	393
139*	3,4-Difluorophenyl	415
140*	4-Chlorophenyl	413
141*	2-Cyanophenyl	404

*:Monohydrochloride

Examples 142 to 156

[0134] The compound of Reference example 11 and a corresponding starting compound were subjected to N-alkylation in the same manner as in Reference example 8, and then, the resulting compound was treated with a corresponding isocyanate to carry out cyclization in the same manner as in Example 1 to give the compounds shown in Table 14 and Table 15.

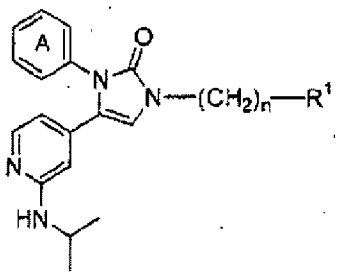
Table 14



Example	R^1	MS ([M+H]$^+$)
142*	4-Tetrahydropyranyl	397
143**	1-Methyl-4-piperidyl	410
144*	Cyclohexyl	395
145*	Cyclopentyl	381
146*	Cyclobutyl	367
147*	4-Piperidyl	396

*:Monohydrochloride ; **:Dihydrochloride

Table 15



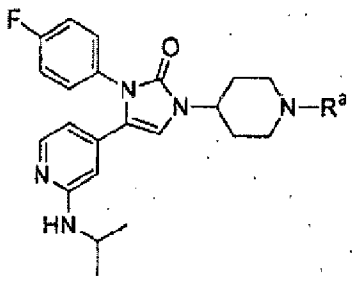
Example	Ring A	n	R^1	MS ([M+H]$^+$)
148*	phenyl	1	trans-4-Hydroxycyclohexyl	407
149*	3-Fluorophenyl	1	trans-4-Hydroxycyclohexyl	425
150*	3-Chlorophenyl	1	trans-4-Hydroxycyclohexyl	441
151*	3-Methylphenyl	1	trans-4-Hydroxycyclohexyl	421
152*	3-Methoxyphenyl	1	trans-4-Hydroxycyclohexyl	437
153*	2,4-Difluorophenyl	1	trans-4-Hydroxycyclohexyl	443
154*	3,4-Difluorophenyl	1	trans-4-Hydroxycyclohexyl	443
155*	4-Chlorophenyl	1	trans-4-Hydroxycyclohexyl	441
156*	2-Carbamoylphenyl	0	Isopropyl	380

*:Monohydrochloride

Examples 157 to 161

[0135] By using the compound of Example 147, it was reacted with a corresponding starting compound to carry out acylation in the same manner as in Example 14 to give the compounds of Examples 157 and 158 shown in Table 16. Also, by using the compound of Example 147, it was reacted with a corresponding starting compound to carry out N-alkylation in the same manner as in Reference example 10 to give the other compounds shown in Table 16. Incidentally, in synthesis of the compound of Example 160, t-butyl bromoacetate was used as a corresponding starting compound, and after the reaction, the ester was hydrolyzed under the same conditions as in Example 80.

Table 16.



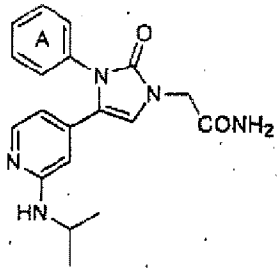
Example	R^a	MS ([M+H]$^+$)
157*	Acetyl	438
158*	Ethoxycarbonyl	468
159**	Carbamoylmethyl	453
160**	Carboxymethyl	454
161**	N-Methylcarbamoylmethyl	467

*:Monohydrochloride ; **:Dihydrochloride

Examples 162 to 168

[0136] By using the compound of Reference example 11, it was reacted with a corresponding starting compound to carry out N-alkylation in the same manner as in Reference example 10, and then, the resulting compound was subjected to cyclization in the same manner as in Example 1 to give the compound of Table 17.

Table 17

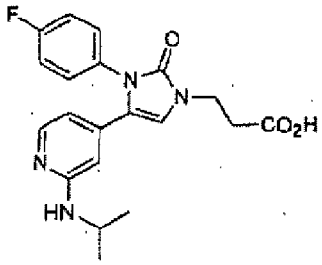


Example	Ring A	MS ([M+H]+)
162*	3-Fluorophenyl	370
163*	3-Chlorophenyl	386
164*	3-Methylphenyl	366
165*	3-Trifluoromethylphenyl	420
166*	Phenyl	352
167*	2,4-Difluorophenyl	388
168*	4-Chlorophenyl	386

*:Monohydrochloride

Example 169

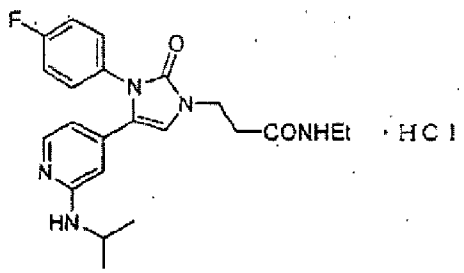
[0137]



[0138] The compound (2.12 g) of Reference example 12 was subjected to cyclization in the same manner as in Example 1 and simultaneously t-butyl ester was hydrolyzed to give 1.28 g of the title compound.
MS 385 ([M+H]+)

Example 170

[0139]



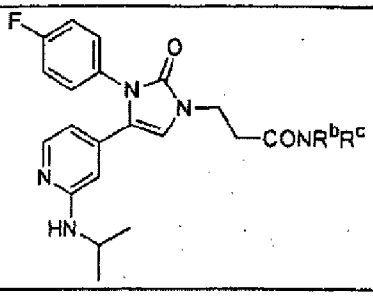
(1) A mixture comprising 100 mg of the compound of Example 169, 48 mg of 1-hydroxybenzotriazole, 60 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1 ml of methylene chloride was stirred at room temperature for one hour. To the reaction mixture was added 1 ml of a 2N ethylamine-THF solution, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was successively washed with water, a saturated aqueous sodium bicarbonate solution and brine, and dried over anhydrous magnesium sulfate. To the residue obtained by concentration under reduced pressure was added diethyl ether to collect colorless crystal by filtration.

(2) The compound obtained in (1) was dissolved in 2 ml of a mixed solvent comprising chloroform-methanol, and after adding 0.2 ml of 4N hydrochloric acid-ethyl acetate, and the resulting mixture was concentrated under reduced pressure. To the residue was added ethyl acetate and collected by filtration to give 75 mg of the title compound.
MS 412([M+H]$^+$)

Examples 171 to 173

[0140] The compound of Example 169 was reacted with a corresponding amine in the same manner as in Example 170 to give the compounds shown in Table 18.

Table 18



Example	NR^bR^c	MS ([M+H]$^+$)
171*	Amino	384
172*	Methylamino	398
173*	Dimethylamino	412

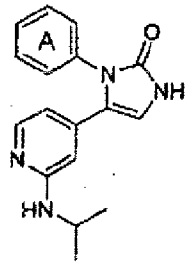
*:Monohydrochloride

Examples 174 to 178

[0141] The compound of Reference example 11 was reacted with a corresponding isocyanate in the same manner

as in Example 1 to give the compounds shown in Table 19.

Table 19

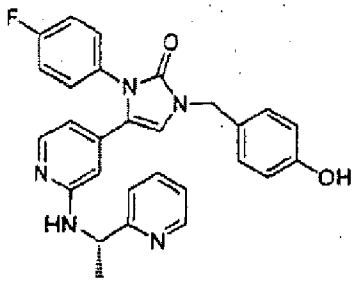


Example	Ring A	MS ([M+H]$^+$)
174*	3,4-Difluorophenyl	331
175*	4-Methoxyphenyl	325
176*	3-Trifluoromethylphenyl	363
177*	3-Chlorophenyl	329
178*	3-Methylphenyl	309

*: Monohydrochloride

Example 179

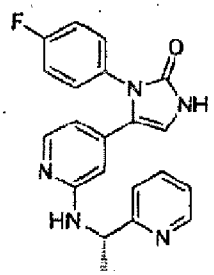
[0142]



[0143] To 5 ml of 25% HBr-acetic acid solution was added 490 mg of the compound of Example 57, and the mixture was stirred at 70°C for 15 hours. After cooling the reaction mixture, an aqueous sodium bicarbonate solution was added to neutralize the mixture, and the resulting mixture was extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography to give 237 mg of the title compound as colorless powder.
MS 482 ([M+H]$^+$)

Example 180

[0144]

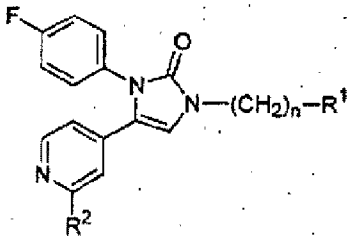


[0145] To 200 mg of the compound of Example 179 was added 2 ml of 25% HBr-acetic acid solution, and the mixture was stirred under heating at 80°C for 3 days. After cooling the reaction mixture, an aqueous sodium bicarbonate solution was added thereto to make alkaline, and the mixture was extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography to give 71 mg of the title compound as colorless powder.
MS 376 ([M+H]$^+$)

Examples 181 to 183

[0146] By using the compound of Example 55, it was reacted in the same manner as in Examples 179 and 180 to give the compounds of Examples 181 and 182 shown in Table 20. Also, in the same manner as in Example 55, a corresponding compound having isobutylamino group was synthesized, and subsequently the compound was reacted in the same manner as in Example 180 to give the compound of Example 183.

Table 20

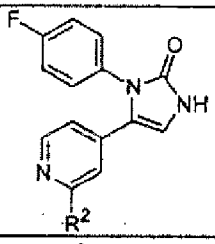


Example	R^1	n	R^2	MS ([M+H]$^+$)
181	4-Hydroxyphenyl	1	Isopropylamino	419
182	Hydrogen atom	0	Isopropylamino	313
183	Hydrogen atom	0	Isobutylamino	327

Examples 184 and 185

[0147] By using the compound of Example 70 or the compound of Example 105, it was reacted under the same conditions (conc. hydrochloric acid was used in place of HBr-acetic acid) as in Example 179 to give the compounds shown in Table 21.

Table 21

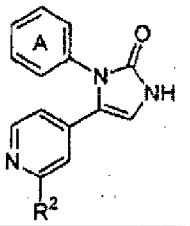


Example	R^2	MS ([M+H]$^+$)
184	trans-4-Hydroxycyclohexylamino	369
185	trans-4-Aminocyclohexylamino	368

Examples 186 to 197

[0148] The compound of Reference example 13 was subjected to amination in the same manner as in Example 4, and then, reacted with a corresponding isocyanate in the same manner as in Example 1, and, if necessary, subjected to acetylation according to the conventional manner to give the compounds shown in Table 22.

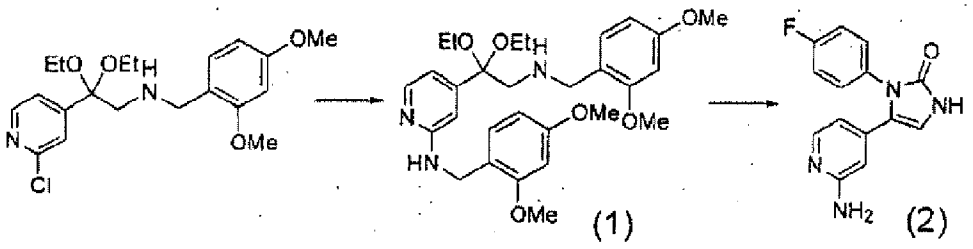
Table 22



Example	Ring A	R^2	MS ($[M+H]^+$)
186	3-Fluorophenyl	Isobutylamino	327
187	3-Fluorophenyl	Isopropylamino	313
188	2,4-Difluorophenyl	Isopropylamino	331
189	2-Fluorophenyl	Isopropylamino	313
190	2,4-Difluorophenyl	Isobutylamino	345
191	3-Methoxyphenyl	Isopropylamino	325
192	Phenyl	Isopropylamino	295
193	2-Fluorophenyl	trans-4-Acetoxycyclohexylamino	411
194	3-Fluorophenyl	trans-4-Acetoxycyclohexylamino	411
195	2,4-Difluorophenyl	trans-4-Acetoxycyclohexylamino	429
196	Phenyl	trans-4-Acetoxycyclohexylamino	393
197	3-Methoxyphenyl	trans-4-Acetoxycyclohexylamino	423

Example 198

[0149]

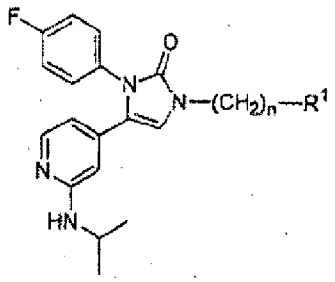


[0150] The compound (6.30 g) of Reference example 13 was reacted with 2, 4-dimethoxybenzylamine in the same manner as in Example 4 to give Compound (1). Then, Compound (1) was treated in the same manner as in Example 1 to give 744 mg of Compound (2).
MS 271 ($[M+H]^+$)

Examples 199 to 221

[0151] The compound of Example 182, 192, 189, 187 or 188 was reacted with a corresponding halide in the same manner as in Reference example 1(6) to subject to alkylation to give the compounds shown in Tables 23 and 24. Incidentally, the compound of Example 211 was synthesized by protecting the amino group with a t-butoxycarbonyl for the reaction and deprotecting in the same manner as in Example 80. Also, the compound of Example 214 was synthesized by eliminating a methoxymethyl group of the compound of Example 213 in the same manner as in Example 81.

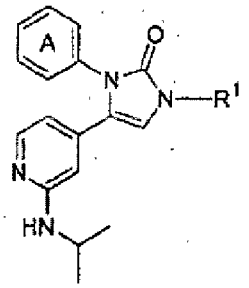
Table 23



Example	n	R^1	MS ([M+H]$^+$)
199*	0	Methyl	327
200	0	3-hydroxypropyl	371
201	0	Butyl	369
202*	0	2-Methoxyethyl	371
203*	0	Carbamoylmethyl	370
204	0	Ethyl	341
205*	0	Isopropyl	355
206*	1	Cyclobutyl	381
207*	0	Isobutyl	369
208*	0	Cyanomethyl	352
209*	0	Isopentyl	383
210*	1	Cyclopropyl	367
211**	0	3-Aminopropyl	370
212*	0	Propyl	355
213	0	2-Methoxymethoxyethyl	401
214*	0	2-Hydroxyethyl	357
215*	0	1-Carbamoylethyl	384

*:Monohydrochloride ; **:Dihydrochloride

Table 24



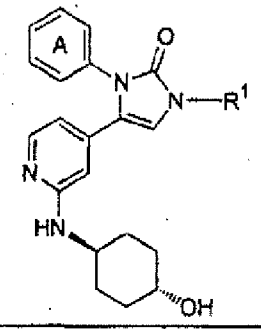
Example	Ring A	R^1	MS ([M+H]$^+$)
216	Phenyl	Ethyl	323
217	2-Fluorophenyl	Ethyl	341
218	3-Fluorophenyl	Ethyl	341
219*	2,4-Difluorophenyl	Ethyl	359
220	Phenyl	Methoxymethyl	339
221	2,4-Difluorophenyl	Methoxymethyl	375

*:Monohydrochloride

Examples 222 to 225

[0152] The corresponding starting materials obtained in the same manner as in Example 192 were reacted with a corresponding halide in the same manner as in Reference example 1(6) to subject to alkylation to give the compounds shown in Table 25.

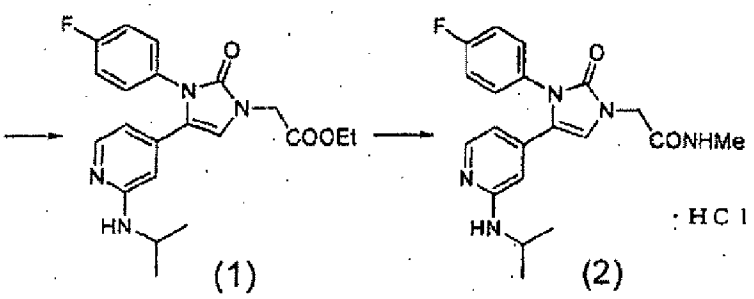
Table 25



Example	Ring A	R^1	MS ([M+H]$^+$)
222	3-Fluorophenyl	Ethyl	397
223	2,4-Difluorophenyl	Ethyl	415
224	3-Methoxyphenyl	Ethyl	409
225	2,4-Difluorophenyl	Methoxymethyl	431

Example 226

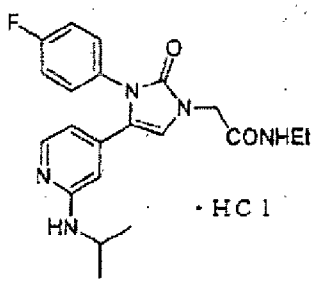
[0153]



[0154] The compound of Example 182 was reacted with a corresponding halide in the same manner as in Reference example 1(6) to subject to alkylation to synthesize Compound (1). A mixture comprising 226 mg of Compound (1), 1.1 ml of 1N aqueous NaOH solution and 1.1 ml of ethanol was stirred at room temperature for 3 hours. The resulting mixture was neutralized with 1N hydrochloric acid, and precipitated crystals were collected by filtration to give 184 mg of the corresponding carboxylic acid. 148 mg of the obtained crystals was reacted with methylamine in the same manner as in Example 170 to give 96 mg of Compound (2).
MS 384 ([M+H]$^+$)

Example 227

[0155]

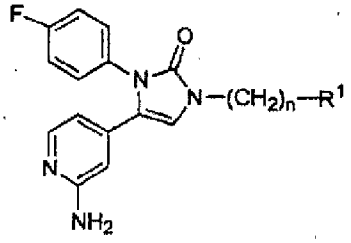


[0156] The compound of Example 226(1) was reacted with ethylamine in the same manner as in Example 226 (2) to give the title compound.
MS 398 ([M+H]$^+$)

Examples 228 and 229

[0157] The compound of Reference example 1(5) was reacted with a corresponding compound in the same manner as in Reference example 1(6), subsequently the resulting compound was treated in the same manner as in Examples 5 and 13 to give the compounds shown in Table 26. Incidentally, the compound of Example 229 was synthesized by using 2,4-dimethoxybenzyl in place of 4-methoxybenzyl, and deprotecting with conc. hydrochloric acid/THF (70°C).

Table 26

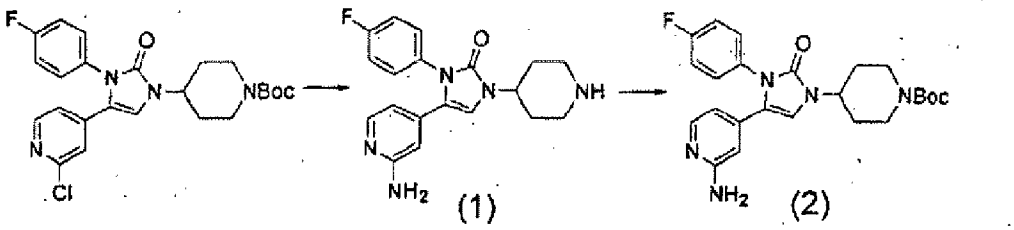


Example	n	R^1	MS ([M+H]$^+$)
228	1	2-Fluorophenyl	379
229	0	Isopropyl	313

*:Monohydrochloride

Example 230

[0158]

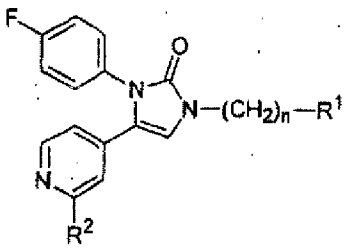


[0159] The compound (1.5 g) of Reference example 9 was reacted with 2,4-dimethoxybenzylamine and deprotected in the same manner as in Example 229 to give 707 mg of Compound (1). This compound (1) (707 mg) was dissolved in 7 ml of THF, and 410 mg of Boc_2O was added and the resulting mixture was stirred at room temperature for 30 minutes. After concentration under reduced pressure, diethyl ether was added to the mixture and precipitates were collected by filtration to give 770 mg of Compound (2) as colorless crystals.
MS 454 ($[M+H]^+$)

Examples 231 to 242

[0160] By using the compounds of Example 13 and Examples 228 to 230, they were reacted with an acid halide in the same manner as in Example 14, and if necessary, by removing t-butoxycarbonyl in the same manner as in Example 80 to give the compounds shown in Table 27.

Table 27

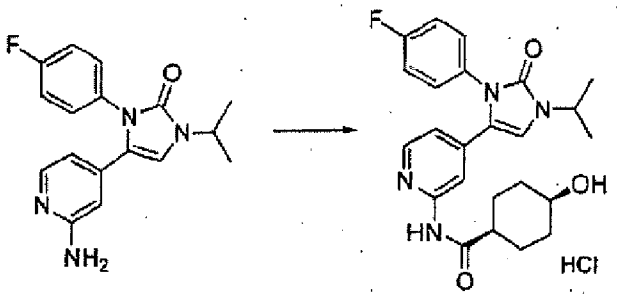


Example	n	R^1	R^2	MS ([M+H]$^+$)
231	1	2-Cyanophenyl	Acetylamino	428
232	1	2-Cyanophenyl	2-Pyridylcarbonylamino	491
233	1	2-Fluorophenyl	Acetylamino	421
234	1	2-Fluorophenyl	Propionylamino	435
235	1	2-Fluorophenyl	Isobutyrylamino	449
236	1	2-Fluorophenyl	Methoxycarbonylacetylamino	479
237	1	2-Fluorophenyl	3-Methoxypropionyl-amino	465
238	1	2-Fluorophenyl	Cyclopropylcarbonyl-amino	447
239*	0	Isopropyl	Cyclopropylcarbonyl-amino	381
240*	0	Isopropyl	Cyclopentylcarbonyl-amino	409
241**	0	4-Piperidyl	Isobutyrylamino	424
242**	0	4-Piperidyl	Cyclopropylcarbonyl-amino	422

*:Monohydrochloride ; **:Dihydrochloride

Example 243

[0161]

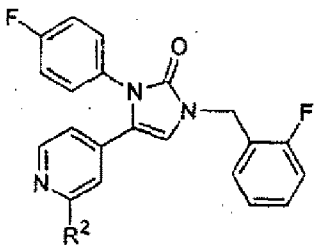


[0162] In 45 ml of acetonitrile was dissolved 4.5 g of cis-4-(methoxymethoxy) cyclohexane carboxylic acid, 3.73 g of 1,1'-carbonyldiimidazole was added to the solution, and the mixture was stirred at room temperature for one hour. To the mixture were added 4.07 g of the compound of Example 229 and 45 ml of acetonitrile, and the resulting mixture was refluxed under heating for 4 days. Water and an aqueous sodium bicarbonate solution were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, 50 ml of methanol was added to the residue and the mixture was stirred for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to give an amide compound. This compound was treated in the same manner as in Example 81 to obtain 5.26 g of the title compound.
MS 439 ([M+H]$^+$)

Examples 244 to 263

[0163] By using the compounds of Examples 228 to 230, they were reacted with a corresponding carboxylic acid in the same manner as in Example 243, and if necessary, by removing t-butoxycarbonyl in the same manner as in Example 80 to give the compounds shown in Tables 28 and 29.

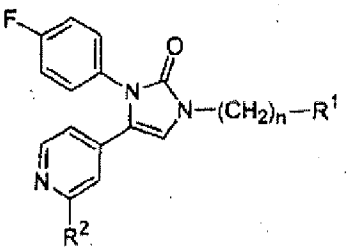
Table 28



Example	R^2	MS ([M+H]$^+$)
244	(Acetylamino)acetylamino	478
245**	(S)-2-Amino-propionylamino	450
246**	(S)-2-Methylamino-propionylamino	464
247**	(S)-2-Amino-3-methoxy-propionylamino	480
248**	3-Amino-propionylamino	450
249**	(S)-2-Pyrrolidinylcarbonylamino	476
250**	cis-4-Amino-cyclohexylcarbonylamino	504
251**	4-Piperidylcarbonylamino	490
252	3-Acetylamino-propionylamino	492
253	(1-Acetyl-4-piperidyl)carbonylamino	532

**:Dihydrochloride

Table 29



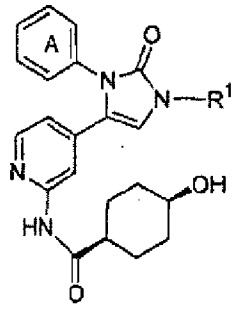
Example	n	R^1	R^2	MS ([M+H]$^+$)
254	1	2-Fluorophenyl	(S)-5-Oxopyrrolidin-2-ylcarbonylamino	490
255*	1	2-Fluorophenyl	cis-4-Hydroxy-cyclohexylcarbonylamino	505
256	1	2-Fluorophenyl	cis-4-Acetylamino-cyclohexylcarbonylamino	546
257	1	2-Fluorophenyl	(S)-1-Acetylpyrrolidin-2-ylcarbonylamino	518
258**	1	2-Fluorophenyl	trans-4-Amino-cyclohexylcarbonylamino	504
259*	1	2-Fluorophenyl	trans-4-Hydroxy-cyclohexylcarbonylamino	505
260*	0	Isopropyl	(S)-5-Oxopyrrolidin-2-ylcarbonylamino	424
261**	0	Isopropyl	cis-4-Amino-cyclohexylcarbonylamino	438
262**	0	4-Piperidyl	trans-4-Hydroxy-cyclohexylcarbonylamino	480
263**	0	4-Piperidyl	cis-4-Hydroxy-cyclohexylcarbonylamino	480

*:Monohydrochloride ; **:Dihydrochloride

Examples 264 to 267

[0164] By using the compounds of Reference examples 14 and 15, they were reacted with a corresponding isocyanate in the same manner as in Example 1, subsequently, the resulting compounds were reacted with a corresponding carboxylic acid in the same manner as in Example 243 to give the compounds shown in Table 30.

Table 30

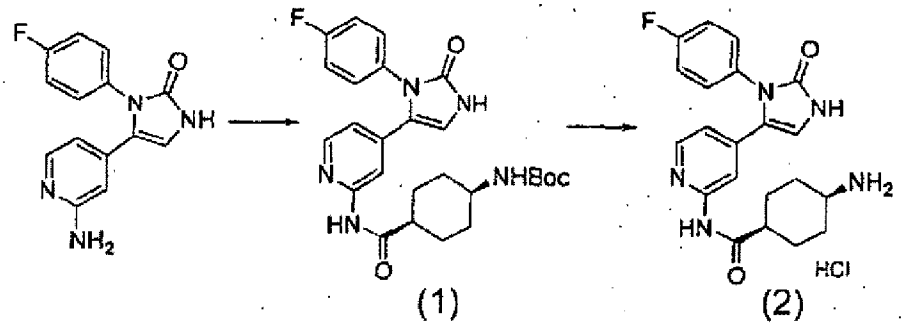


Example	Ring A	R^1	MS ([M+H]$^+$)
264*	3-Chlorophenyl	Isopropyl	455
265*	3-Methylphenyl	Isopropyl	435
266*	3-Chlorophenyl	ethyl	441
267*	3-Methylphenyl	ethyl	421

*:Monohydrochloride

Example 268

[0165]



(1) (2)

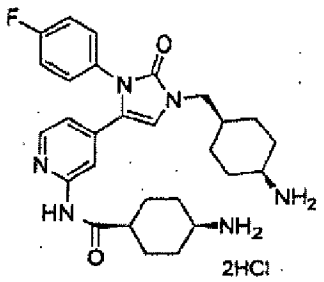
[0166] In 5 ml of acetonitrile were dissolved 540 mg of cis-4-(t-butoxycarbonyl(amino)cyclohexane carboxylic acid and 396 mg of 1,1'-carbonyldiimidazole, and the mixture was stirred at room temperature for an hour. Then, to the reaction mixture were added 200 mg of the compound of Example 198 and 5 ml of acetonitrile, and the mixture was refluxed under heating for 2 days. To the reaction mixture was added an aqueous sodium bicarbonate solution, and the mixture was extracted with chloroform. The extract was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in 5 ml of methanol, and 102 mg of potassium carbonate was added to the mixture. The resulting mixture was diluted with chloroform, washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography to give 255 mg of Compound (1) as colorless powder.
MS 496 ([M+H]$^+$)

[0167] Compound (1) (50 mg) was dissolved in a mixed solvent of methanol and chloroform, 0.5 ml of 4N hydrochloric acid-ethyl acetate solution was added to the mixture, and the resulting mixture was stirred at room temperature over-

night. The reaction mixture was concentrated under reduced pressure to give 46 mg of Compound (2) as yellowish powder.
MS 396 ([M+H]+)

Example 269

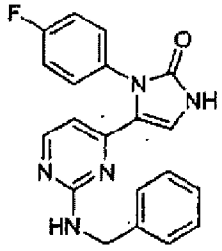
[0168]



[0169] Compound (1) (100 mg) of Example 268 was dissolved in 5 ml of methylene chloride, and to the mixture were added 132 mg of diethylazodicarboxylate (40% solution in toluene), 79 mg of triphenylphosphine and 55 mg of t-butyl (4-hydroxymethylcyclohexyl) carbamate, and the resulting mixture was stirred at room temperature for 21 hours. The reaction mixture was concentrated under reduced pressure, the obtained residue was purified by silica gel column chromatography, and dissolved in 1 ml of methanol. 1 ml of 4N Hydrochloric acid-dioxane was added to the mixture, and the resulting mixture was stirred at room temperature for an hour. The reaction mixture was concentrated to give 118 mg of the title compound as yellowish powder.
MS 507 ([M+H]+)

Example 270

[0170]

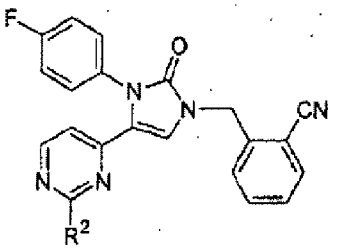


[0171] The compound of Reference example 7(1) was reacted with benzylamine in the same manner as in Example 17 to give the title compound.
MS 362 ([M+H]+)

Examples 271 to 336

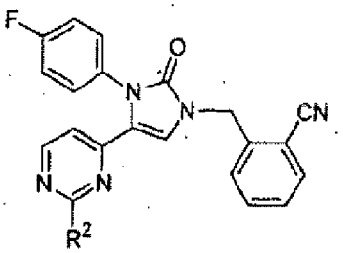
[0172] The compound of Reference example 5 (4) was reacted in the same manner as in Example 2 or Reference example 1(6), oxidized with 3-chloroperoxybenzoic acid in the same manner as in Reference example 6(2), subsequently reacted with a corresponding amine in the same manner as in Example 17, and further, if necessary, t-butoxycarbonyl or methoxymethyl is removed in the same manner as in Example 80 or 81 to give the compounds shown in Tables 31 to 35.

Table 31



Example	R^2	MS ([M+H]$^+$)
271	Benzylamino	477
272	2-Methoxyethylamino	445
273	Cyclopropylamino	427
274	Butylamino	443
275	Isopropylamino	429
276	Ethylamino	415
277	Cyclopropylmethylamino	441
278	trans-4-Hydroxycyclohexylamino	485
279	(S)-1-Hydroxymethyl-ethylamino	445
280	(S)-1-Hydroxymethyl-propylamino	459

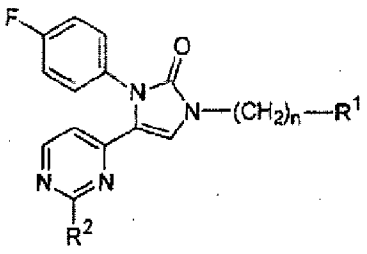
Table 32



Example	R^2	MS ([M+H]$^+$)
281	(S)-1-Hydroxymethyl-2-methylpropyl-amino	473
282	(R)-1-Hydroxymethyl-ethylamino	445
283*	1-Methyl-4-piperidylamino	484
284	1-Benzyl-4-piperidylamino	560
285	1-Ethoxycarbonyl-4-piperidylamino	542
286	1-Hydroxymethyl-cyclopentylamino	485
287	1-t-Butoxycarbonyl-4-piperidylamino	570
288**	4-Piperidylamino	470
289	4-Methoxybenzylamino	507
290**	trans-4-Aminocyclohexylamino	484

*:Monohydrochloride ; **:Dihydrochloride

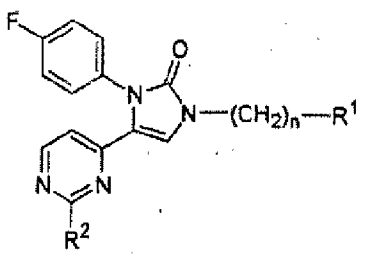
Table 33



Example	n	R^1	R^2	MS ([M+H]$^+$)
291	1	2-Fluorophenyl	trans-4-Hydroxy-cyclohexylamino	478
292	1	2-Methoxyphenyl	trans-4-Hydroxy-cyclohexylamino	490
293**	1	4-Piperidyl	trans-4-Hydroxy-cyclohexylamino	467
294**	1	4-Piperidyl	Isopropylamino	411
295	1	2-Fluorophenyl	Isobutylamino	436
296**	1	4-Piperidyl	Isobutylamino	425
297**	1	2-Fluorophenyl	4-Piperidylamino	463
298*	0	Methyl	trans-4-Hydroxy-cyclohexylamino	384
299**	0	Methyl	trans-4-Aminocy-clohexylamino	383
300*	0	Ethyl	trans-4-Hydroxy-cyclohexylamino	398
301*	0	Ethyl	Isobutylamino	356
302*	0	Isopropyl	trans-4-Hydroxy-cyclohexylamino	412
303**	0	Isopropyl	trans-4-Aminocyclo hexylamino	411
304**	0	ethyl	trans-4-Aminocyclo hexylamino	397
305*	1	cis-4-Hydroxy-cyclohexyl	Isopropylamino	426

*:Monohydrochloride ; **:Dihydrochloride

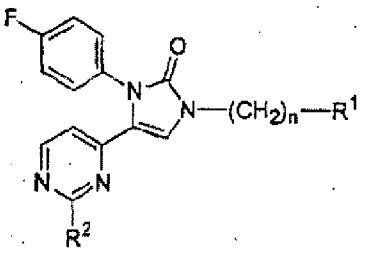
Table 34



Example	n	R^1	R^2	MS ([M+H]$^+$)
306*	1	cis-4-Hydroxycyclohexyl	Isobutylamino	440
307*	1	trans-4-Hydroxycyclohexyl	Isopropylamino	426
308*	1	trans-4-Hydroxycyclohexyl	Isobutylamino	440
309**	1	cis-4-Aminocyclohexyl	Isopropylamino	425
310**	1	cis-4-Aminocyclohexyl	Isobutylamino	439
311**	1	cis-4-Aminocyclohexyl	trans-4-Hydroxycyclohexylamino	481
312*	0	Ethyl	trans-4-acetylaminocyclohexylamino	439
313*	0	Isopropyl	trans-4-acetylaminocyclohexylamino	453
314***	1	cis-4-Aminocyclohexyl	trans-4-Aminocyclohexylamino	480
315**	1	trans-4-Aminocyclohexyl	Isopropylamino	425
316**	1	trans-4-Aminocyclohexyl	Isobutylamino	439
317**	1	trans-4-Aminocyclohexyl	trans-4-Hydroxycyclohexylamino	481
318***	1	trans-4-Aminocyclohexyl	trans-4-Aminocyclohexylamino	480
319*	1	cis-4-Hydroxycyclohexyl	trans-4-Hydroxycyclohexylamino	482
320*	0	Isobutyl	trans-4-Hydroxycyclohexylamino	426

*:Monohydrochloride;**:Dihydrochloride;***:Trihydrochloride

Table 35



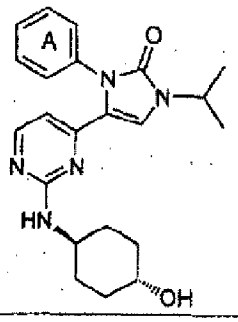
Example	n	R^1	R^2	MS ([M+H]$^+$)
321*	0	propyl	trans-4-Hydroxycyclohexylamino	412
322*	0	butyl	trans-4-Hydroxycyclohexylamino	426
323*	0	Cyanomethyl	trans-4-Hydroxycyclohexylamino	409
324*	0	2-Methoxyethyl	trans-4-Hydroxycyclohexylamino	428
325*	0	3-hydroxypropyl	trans-4-Hydroxycyclohexylamino	428
326*	1	Cyclopropyl	trans-4-Hydroxycyclohexylamino	424
327*	1	Cyclobutyl	trans-4-Hydroxycyclohexylamino	438
328*	0	Ethyl	4-Tetrahydropyranylamino	384
329*	0	Ethyl	(S)-1-Hydroxymethylethylamino	358
330*	0	Ethyl	2-Hydroxy-1,1-dimethylethylamino	372
331*	0	Ethyl	1-Hydroxymethyl-cyclopentylamino	398
332*	0	Ethyl	3-Methoxypropylamino	372
333	0	Isopropyl	2-Hydroxy-1,1-dimethylethylamino	386
334	0	Isopropyl	1-Hydroxymethyl-cyclopentylamino	412
335	0	Ethyl	cis-4-Hydroxycyclohexylamino	398
336	0	Isopropyl	cis-4-Hydroxycyclohexylamino	412

*:Monohydrochloride

Examples 337 to 343

[0173] The compound of Reference example 16 was reacted with a corresponding isocyanate in the same manner as in Example 1, oxidized with 3-chloroperoxybenzoic acid in the same manner as in Reference example 6(2), subsequently reacted with a corresponding amine in the same manner as in Example 17 to give the compounds shown in Table 36.

Table 36



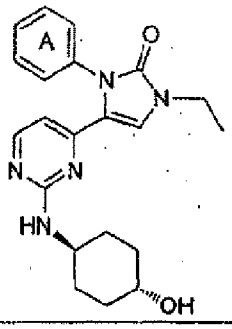
Example	Ring A	MS ([M+H]$^+$)
337*	3-Fluorophenyl	412
338*	3-Methylphenyl	408
339*	Phenyl	394
340*	3-Chlorophenyl	428
341*	4-Chlorophenyl	428
342*	2,4-Difluorophenyl	430
343*	3-Methoxyphenyl	424

*:Monohydrochloride

Examples 344 to 349

[0174] The compound of Reference example 17(3) was reacted with a corresponding isocyanate in the same manner as in Example 1 to give the compounds shown in Table 37.

Table 37

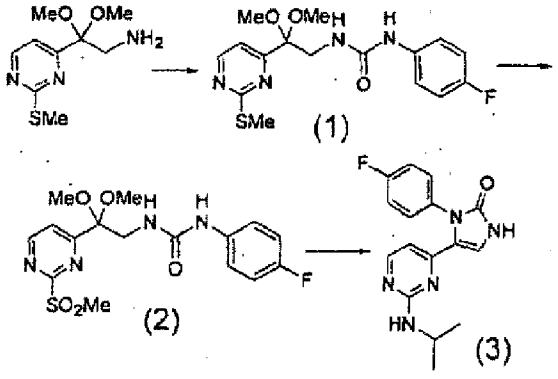


Example	Ring A	MS ([M+H]$^+$)
344*	3-Chlorophenyl	414
345*	3-Methylphenyl	394
346*	3-Trifluoromethylphenyl	448
347*	4-Chlorophenyl	414
348*	Phenyl	380
349*	3-Fluorophenyl	398

*:Monohydrochloride

Example 350

[0175]



(1) To 300 ml of a diethyl ether solution containing 52.0 g of the compound of Reference example 5(3) was added dropwise 100 ml of a diethyl ether solution containing 30.2 g of 4-fluorophenyl isocyanate under ice-cooling, and the mixture was stirred at room temperature for 30 minutes. After concentration under reduced pressure, diisopropyl ether was added to the reaction mixture and crystals were collected by filtration to give 75.0 g of Compound (1) as colorless crystals.

(2) In chloroform was dissolved 30.0 g of Compound (1), and under ice-cooling, 46.4 g of 3-chloroperoxybenzoic

acid was added to the solution and the mixture was stirred at room temperature for 2 hours. After concentration under reduced pressure, diethyl ether was added to the reaction mixture and crystals were collected by filtration to give 30.8 g of Compound (2) as colorless crystals.

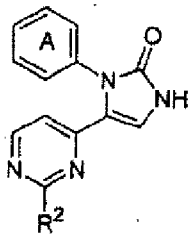
(3) To the compound obtained by treating 20.0 g of Compound (2) with a corresponding starting material in the same manner as in Example 17 was added 100 ml of conc. hydrochloric acid, and the mixture was stirred at room temperature overnight. A 2N aqueous sodium hydroxide solution was added to the mixture to neutralize the same, ethyl acetate was added to the same and after stirring, precipitated crystals were collected by filtration to give 12.4 g of the title compound as colorless crystals.

MS 314 ($[M+H]^+$)

Examples 351 to 354

[0176] The compound of Reference example 5(3) and a corresponding starting material were treated in the same manner as in Example 350 to give the compounds shown in Table 38.

Table 38



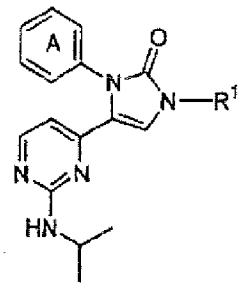
Example	Ring A	R^2	MS ($[M+H]^+$)
351	4-Fluorophenyl	trans-4-Hydroxycyclohexylamino	370
352*	4-Fluorophenyl	Isobutylamino	328
353	2,4-Difluorophenyl	Isopropylamino	332
354	Phenyl	Isopropylamino	296

*:Monohydrochloride

Examples 355 to 367

[0177] By using the compound of Example 350, 353 or 354, or the compound produced by the same manner as in Example 350, they were treated in the same manner as in Reference example 1(6) to give the compounds shown in Table 39.

Table 39



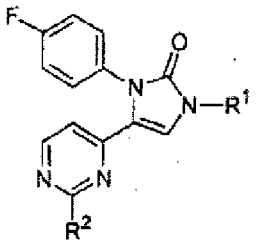
Example	Ring A	R^1	MS ([M+H]$^+$)
355*	4-Fluorophenyl	Methyl	328
356*	4-Fluorophenyl	Ethyl	342
357*	4-Fluorophenyl	Methoxymethyl	358
358	2,4-Difluorophenyl	Ethyl	360
359	Phenyl	Ethyl	324
360	4-Chlorophenyl	Ethyl	358
361	3-Fluorophenyl	Ethyl	342
362	3-Methoxyphenyl	Ethyl	354
363	2,4-Difluorophenyl	Methoxymethyl	376
364	Phenyl	Methoxymethyl	340
365	4-Chlorophenyl	Methoxymethyl	374
366*	4-Fluorophenyl	2-Methoxyethyl	372
367*	4-Fluorophenyl	Cyanomethyl	353

*:Monohydrochloride

Examples 368 to 382

[0178] The compound of Reference example 5(4) was reacted in the same manner as in Example 2 or Reference example 1(6), oxidized with 3-chloroperoxybenzoic acid in the same manner as in Reference example 6(2), subsequently reacted with a corresponding amine in the same manner as in Example 17, and if necessary, t-butoxycarbonyl was removed in the same manner as in Example 80 to give the compounds shown in Table 40.

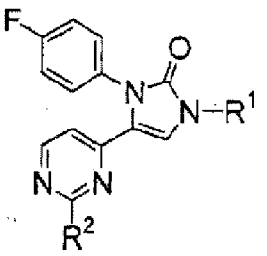
Table 40



Example	R^1	R^2	MS ([M+H]$^+$)
368*	Ethyl	cis-4-Hydroxymethyl-cyclohexylamino	412
369*	Ethyl	trans-4-Hydroxymethyl-cyclohexylamino	412
370*	Ethyl	3-Hydroxy-2,2-dimethyl-propylamino	386
371*	Isopropyl	cis-4-Hydroxymethyl-cyclohexylamino	426
372*	Isopropyl	trans-4-Hydroxymethyl-cyclohexylamino	426
373*	Isopropyl	3-Hydroxy-2,2-dimethyl-propylamino	400
374*	Isopropyl	(S)-2-Hydroxypropylamino	372
375*	Isopropyl	(R)-2-Hydroxypropylamino	372
376*	Isopropyl	1-Hydroxycyclohexyl-methylamino	426
377**	Isopropyl	2-Hydroxy-1-hydroxy-methyl-1-methylethyl-amino	402
378**	Isopropyl	4-Piperidyl	397
379**	Isopropyl	(S)-1-(2-Pyridyl)ethyl-amino	419
380*	Isopropyl	(1S,2S)-2-Hydroxycyclo-pentylamino	398

*:Monohydrochloride ; **:Dihydrochloride

Table 40 (Continued)



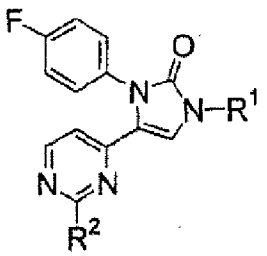
Examples	R^1	R^2	MS ($[M+H]^+$)
381*	Ethyl	(1S,2S)-2-Hydroxycyclopentylamino	384
382*	Ethyl	trans-4-Carbamoylcyclohexylamino	425

*:Monohydrochloride ; **:Dihydrochloride

Examples 383 to 386

[0179] The compound of Example 303 or 304 was subjected to methanesulfonylation or methoxycarbonylation according to the conventional methods to give the compounds shown in Table 41.

Table 41



Examples	R^1	R^2	MS ([M+H]$^+$)
383*	Isopropyl	trans-4-Methanesulfonyl-aminocyclohexylamino	489
384*	Isopropyl	trans-4-Methoxycarbonyl-aminocyclohexylamino	469
385*	Ethyl	trans-4-Methanesulfonyl-aminocyclohexylamino	475
386*	Ethyl	trans-4-Methoxycarbonyl-aminocyclohexylamino	455

*:Monohydrochloride

Example 387

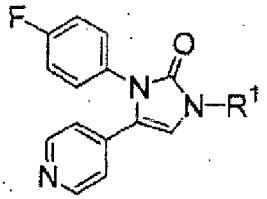
[0180]

[0181] The compound of Example 1 (100 mg), 4-acetylphenylboronic acid (129 mg), copper (II) acetate (72 mg) and triethylamine (220 µl) were suspended in 10 ml of methylene chloride, and the suspension was stirred at room temperature for 24 hours. To the reaction mixture, 28% aqueous ammonia was added and the mixture was extracted with chloroform, washed with brine, and dried over anhydrous magnesium sulfate. The resultant mixture was concentrated under reduced pressure, and ether was added to the residue and precipitated crystals were collected by filtration to give 92 mg of the title compound. Melting point: 206°C (decomposed)

Examples 388 to 389

[0182] The compound of Example 1 and the corresponding starting materials were reacted in the same manner as in Example 387 to give the compounds shown in Table 42.

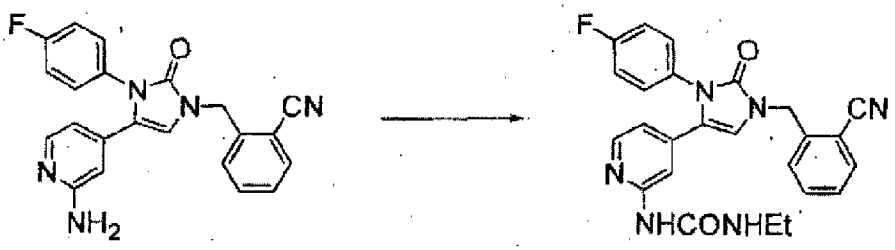
Table 42



Examples	R^1	Melting point (℃)
388	4-Pyridyl	189
389	3-Thienyl	193-195

Example 390

[0183]

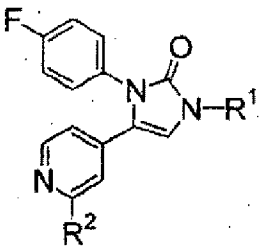


[0184] To a solution of the compound of Example 13 (50 mg) in THF was added ethyl isocyanate (12 µl), and the mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography to give 19 mg of the title conpound as colorless crystal. Melting point: 209 - 210°C

Examples 391 to 394

[0185] The compound of Example 16 and the compounds prepared in the same manner as in Example 16 were subjected to hydrolysis followed by amidation according to the conventional methods, or subjected to reduction followed by mesylation and dimethylamination, to give the compounds shown in Table 43.

Table 43

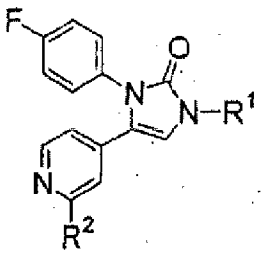


Examples	R^1	R^2	Melting point (℃)
391	2-Cyanobenzyl	Carboxy	135 (decomposed)
392	2-Cyanobenzyl	Carbamoyl	209-210 (decomposed)
393	2-Fluorobenzyl	Hydroxymethyl	157-158 (decomposed)
394	2-Fluorobenzyl	Dimethylamino-methyl	231-236 (decomposed)

Examples 395 to 398

[0186] The corresponding starting materials were reacted in the same manner as in Example 368 to give the compounds shown in Table 44.

Table 44

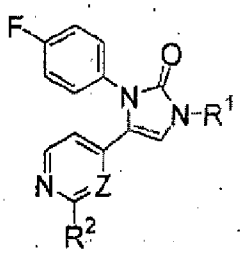


Example	R^1	R^2	MS ([M+H]$^+$)
395*	Ethyl	trans-4-Hydroxycyclohexyl-methylamino	412
396*	Isopropyl	trans-4-Hydroxycyclohexyl-methylamino	426
397*	Ethyl	cis-4-Hydroxycyclohexyl-methylamino	412
398*	Isopropyl	cis-4-Hydroxycyclohexyl-methylamino	426

*:Monohydrochloride

[0187] According to the production methods described in the above Examples and the present specification and methods conventionally employed in the field of organic synthetic chemistry, compounds, which is respectively combined with each of the substitutents shown in Tables 45 to 51, can be produced.

Table 45



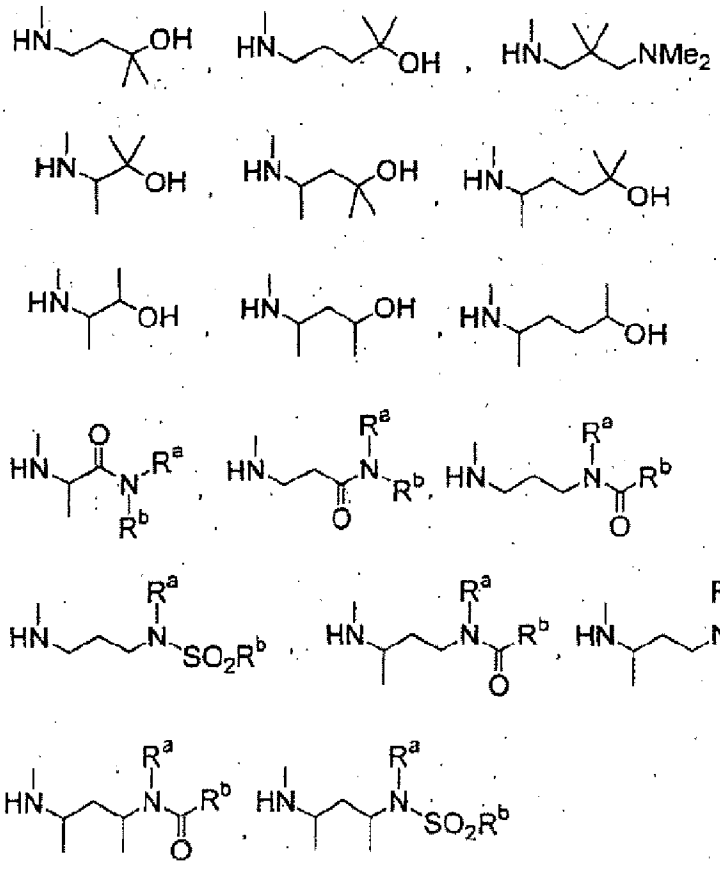
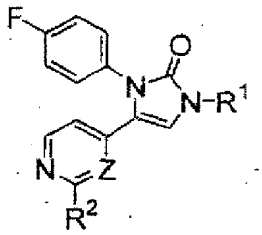
R^1 = methyl, ethyl, isopropyl,  , 
Z = CH, N
R^2 = 
R^a, R^b = each independently, hydrogen, C_1~C_3 alkyl

Table 46



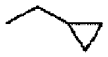
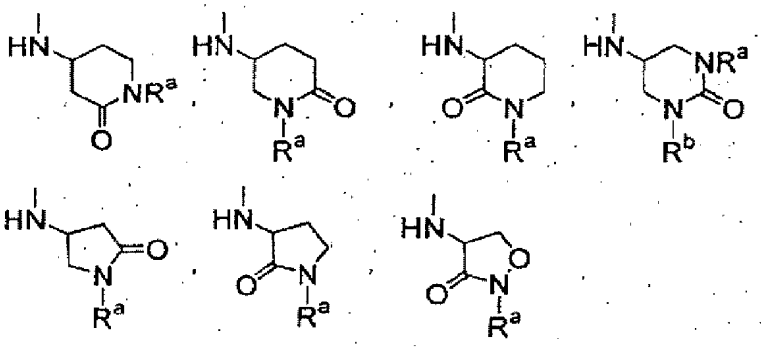
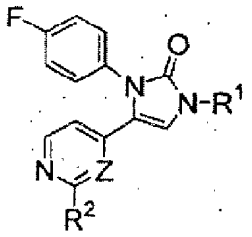
R^1 = methyl, ethyl, isopropyl,  , 	
Z = CH, N	
R^2 = 	
R^a, R^b = each independently, hydrogen, C_1~C_3 alkyl	

Table 48



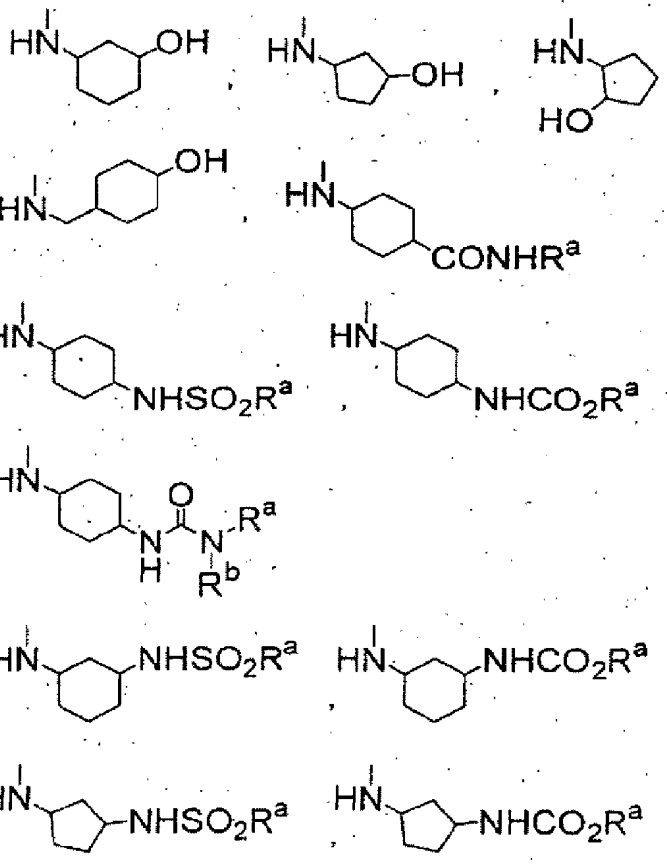
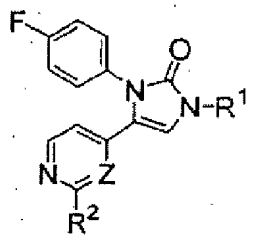
R^1 = methyl, ethyl, isopropyl,  , 
Z = CH, N
R^2 = 
R^a, R^b = each independently, hydrogen, C_1~C_3 alkyl

Table 49



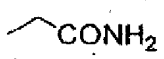
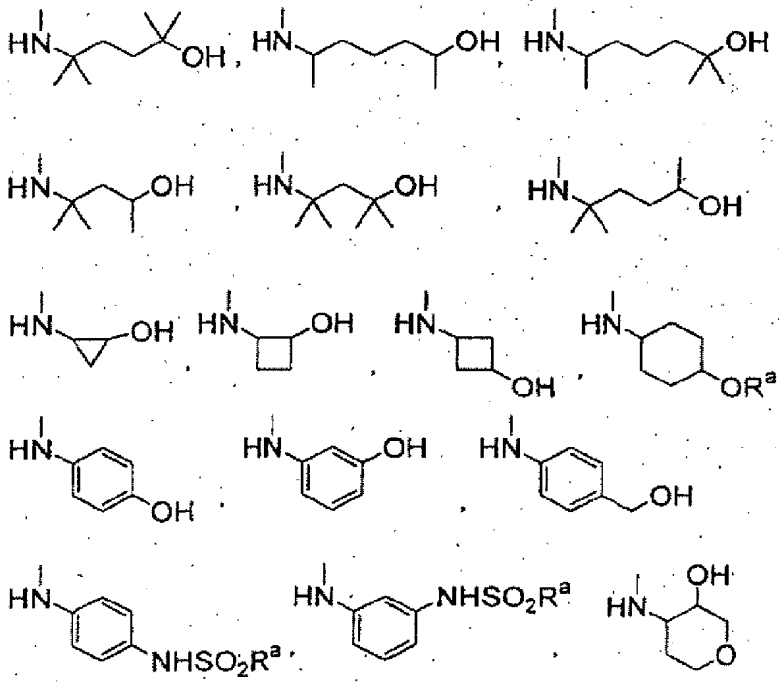
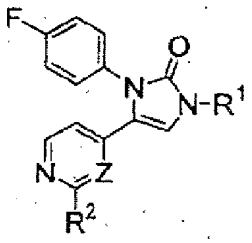
R^1 = methyl, ethyl, isopropyl,  , 
Z = CH, N
R^2 = 
R^a, R^b = each independently, hydrogen, C_1~C_3 alkyl

Table 50



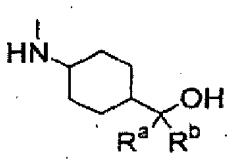
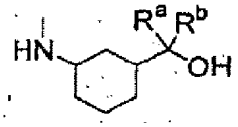
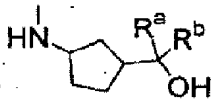
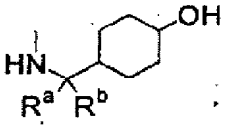
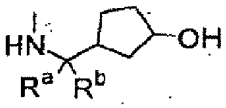
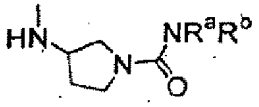
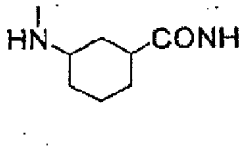
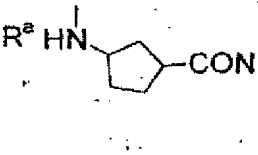
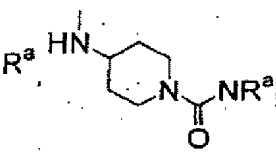
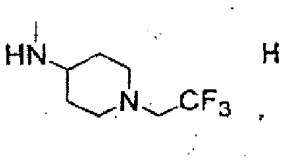
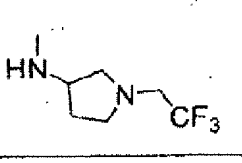
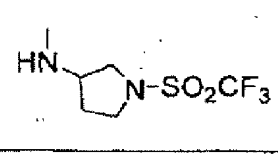
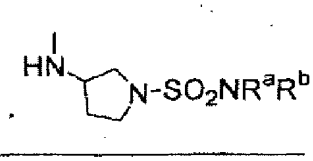
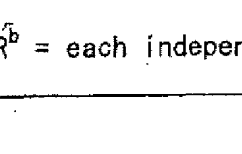
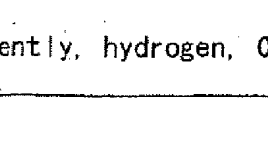
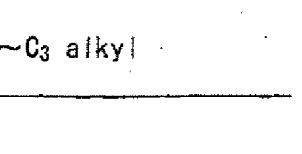
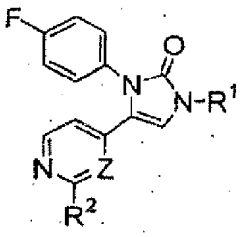
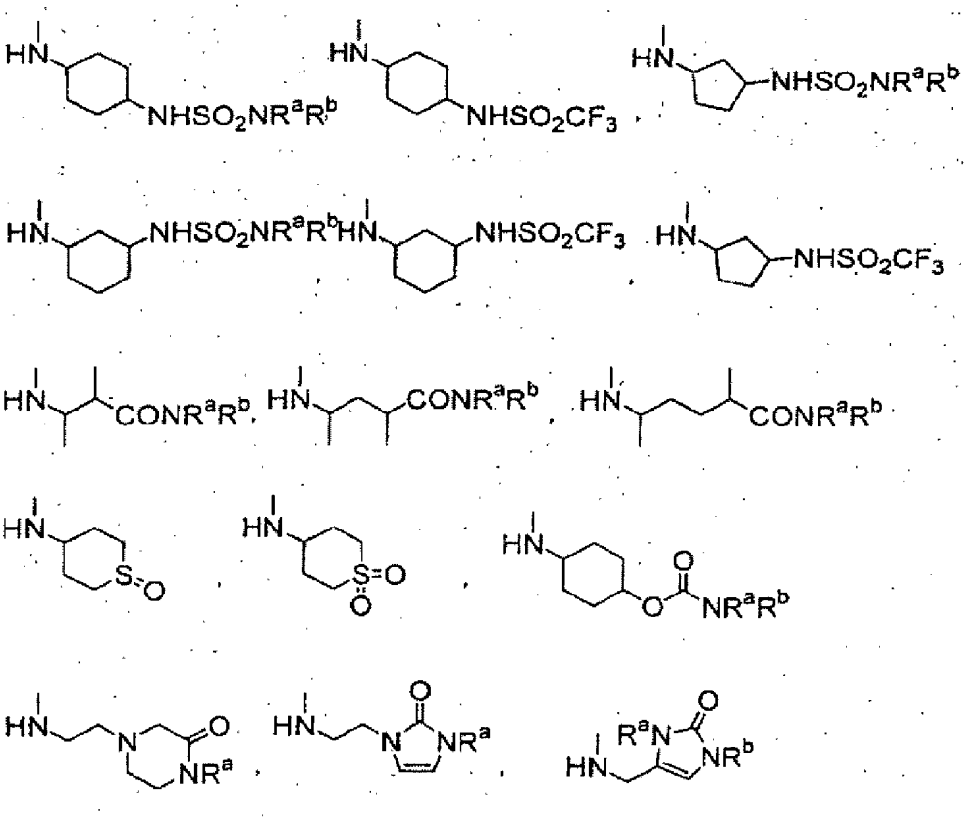
R^1 = methyl, ethyl, isopropyl,  , 
Z = CH, N
R^2 =  ,  ,     ,  ,     ,  ,        ,  ,     ,  , 
R^a, R^b = each independently, hydrogen, C_1~C_3 alkyl

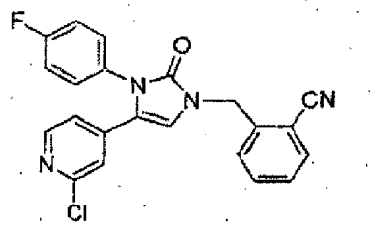
Table 51



R^1 = methyl, ethyl, isopropyl,  , 	
Z = CH, N	
R^2 = 	
R^a, R^b = each independently, hydrogen, C_1~C_3 alkyl	

Reference example 1

[0188]



(1) In 440 ml of THF was suspended 22 g of 2-chloroisonicotinic acid, and under nitrogen flow, the mixture was cooled to -70°C or lower, 245 ml of methyl lithium (1.14 M solution in diethyl ether) was added dropwise to the mixture. After stirring at the same temperature for an hour, a temperature of the mixture was raised to 0°C over an hour, and stirred at the same temperature for further an hour. To the reaction mixture was added 500 ml of water, and the reaction mixture was extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. Activated charcoal was added to the mixture, and after filtration, the filtrate was concentrated under reduced pressure to give 19.5 g of 4-acetyl-2-chloropyridine as colorless crystals. Melting point: 36°C.

(2) In 550 ml of ethanol were suspended 55.1 g of the compound obtained in (1), 49.2 g of hydroxylamine hydrochloride and 58.1 g of sodium acetate, and the mixture was refluxed under heating for an hour. After cooling the mixture to room temperature by allowing to stand, ethanol was distilled away under reduced pressure and precipitated crystals were collected by filtration and washed with water. The crystals were air-dried at 60°C overnight to give 55 g of 1-(2-chloropyridin-4-yl)ethanone oxime as colorless crystals. Melting point: 143°C.

(3) In methylene chloride were suspended 105 g of the compound obtained in (2) and 123 g of tosyl chloride, and under ice-cooling, 94 ml of triethylamine was added dropwise to the mixture, and the mixture was raised to room temperature and stirred for 4 hours. To the reaction mixture was added 500 ml of water, and the mixture was extracted with methylene chloride, washed with brine and dried over magnesium sulfate. After filtration, the mixture was concentrated under reduced pressure, and the resulting crystals were collected by filtration and washed with isopropyl ether to give 192 g of 1-(2-chloropyridin-4-yl)ethanone oxime tosylate as colorless crystals. Melting point: 153°C.

(4) Under nitrogen flow, 3.11 g of sodium metal was added to 220 ml of anhydrous ethanol at room temperature, and the mixture was dissolved under stirring. The solution was ice-cooled, and 40 g of the compound obtained in (3) was added thereto, then the mixture was stirred at room temperature for an hour. To the mixture was added 220 ml of anhydrous ether, and insoluble matters were removed. To the filtrate was added 62 ml of 4N hydrochloric acid/dioxane solution under ice-cooling and the mixture was stirred for 15 minutes. After the reaction mixture was concentrated under reduced pressure, the residue was dissolved in water and the solution was made alkaline by addition of potassium carbonate. This mixture was extracted with ethyl acetate several times, and the combined extracts were washed with brine and dried over magnesium sulfate. After concentration under reduced pressure, 100 ml of hexane was added to the residue and red insoluble matters were removed by filtration. The filtrate was concentrated under reduced pressure, hexane was again added to the concentrate and insoluble matters were removed by filtration through Celite. The filtrate was concentrated under reduced pressure and dried by a vacuum pump to give 26.9 g of 2-(2-chloropyridin-4-yl)-2,2-diethoxyethylamine as reddish oily product.

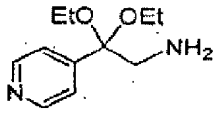
(5) A solution, in which 20 g of the compound obtained in (4) was dissolved in 50 ml of THF, was water-cooled, and 11.2 g of 4-fluorophenylisocyanate was added dropwise thereto. After dropwise addition, the reaction mixture was concentrated under reduced pressure, and 30 ml of conc. hydrochloric acid was added to the obtained residue and the mixture was stirred at room temperature overnight. The reaction mixture was added to ice-cooled 160 ml of 2N aqueous NaOH solution to neutralize the mixture, and after collecting the precipitated crystals by filtration, the crystals were washed with water and ether. The crystals were air-dried at 60°C to give 22.3 g of 5-(2-chloropyridin-4-yl)-1-(4-fluorophenyl)-4-imidazolin-2-one as colorless crystals. Melting point: 270°C.

(6) In 50 ml of DMF was suspended 10 g of the compound obtained in (5), and under ice-cooling, 1.46 g of 63% sodium hydride was added to the suspension, then the mixture was stirred at room temperature for 30 minutes. The mixture was again ice-cooled, and after adding 7.44 g of 2-cyanobenzyl bromide, the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into 250 ml of ice-cold water, extracted with ethyl acetate. The extract was washed with water and brine, and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography to give 11.4 g

of 4-(2-chloropyridin-4-yl)-3-(4-fluorophenyl)-1-(2-cyanobenzyl)-4-imidazolin-2-one as colorless crystals. Melting point: 109°C.

Reference example 2

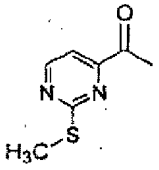
[0189]



[0190] By using 4-acetylpyridine (commercially available product) as a starting material, the same treatments as in Reference examples 1(2) to (4) were carried out to give 2,2-diethoxy-2-pyridin-4-yl ethylamine as brownish oily product.

Reference example 3

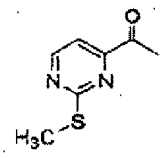
[0191]



(1) A mixture of 100 g of 3,3-dimethoxy-2-butanone and 99.2 g of N,N-dimethylformamide dimethylacetal was stirred at 100°C for 42 hours. After cooling the reaction mixture, the mixture was concentrated under reduced pressure to give 141 g of 1-dimethylamino-4,4-dimethoxy-1-penten-3-one.
(2) In 800 ml of methanol was dissolved 141 g of the compound obtained in (1), and after adding 114 g of thiourea and 292 g of 28% sodium methoxide-methanol, the mixture was stirred at 70°C for 3 hours. The mixture was ice-cooled, and after adding 215 g of methyl iodide drowise, the mixture was stirred at room temperature for an hour. After concentration of the reaction mixture, water was added to the mixture and the resulting mixture was extracted with ethyl acetate. The organic layer was washed, dried and concentrated to give 142 g of 4-(1,1-dimethoxyethyl)-2-methylsulfanylpyrimidine.
(3) In 570 ml of acetone was dissolved 142 g of the compound obtained in (2), and under ice-cooling, 114 ml of 6M hydrochloric acid was added to the solution and the mixture was stirred at room temperature for 3 hours. After adding 450 ml of water to the mixture, the solvent was removed and the residue was extracted with ethyl acetate. The organic layer was washed, dried and concentrated to give 107 g of 1-(2-methylsulfanylpyrimidin-4-yl)ethanone.

Reference example 4

[0192]



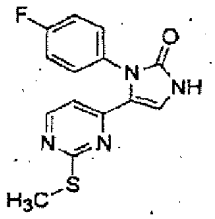
(1) A mixture comprising 16.4 g of 4-chloro-2-methylsulfanylpyrimidine, 38 g of tributyl(1-ethoxyvinyl) tin, 1.43 g of bis (triphenylphosphine)palladium (II) dichloride and 100 ml of DMF was stirred at 80°C for 3 hours. After cooling the reaction mixture, 300 ml of ethyl acetate and 17.8 g of potassium fluoride were added to the mixture, and the resulting mixture was stirred at room temperature overnight. After filtration with Celite, the filtrate was washed,

dried and concentrated. The residue was purified by silica gel column chromatography (hexane:ethylacetate=20:1) to give 18.9 g of 4-(1-ethoxyvinyl)-2-methylsulfanylpyrimidine.

(2) In 200 ml of acetone was dissolved 18.9 g of the compound obtained in (1), 60 ml of 4M hydrochloric acid was added to the solution and the mixture was stirred at room temperature for an hour. The reaction mixture was added to a saturated aqueous sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was washed, dried and concentrated to give 15.9 g of 1-(2-methylsulfanylpyrimidin-4-yl)ethanone.

Reference example 5

[0193]



(1) In 180 ml of methanol was dissolved 17.6 g of the compound obtained in Reference example 3 (3) or Reference example 4 (2), 14.5 g of hydroxylamine hydrochloride and 17.2 g of sodium acetate were added to the solution, and the mixture was refluxed under heating for 30 minutes. After cooling the reaction mixture, the solvent was removed, water was added to the residue and the mixture was extracted with ethyl acetate. The organic layer was washed, dried and concentrated. To the residue was added hexane and the precipitated crystals were collected by filtration to give 18.3 g of 1-(2-methylsulfanylpyrimidin-4-yl)ethanone oxime. Melting point: 150-152°C.

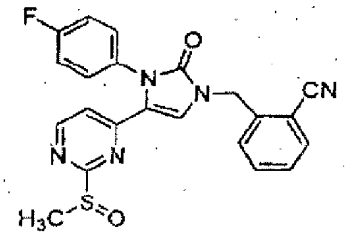
(2) In 1200 ml of methylene chloride was suspended 89 g of the compound obtained in (1), and 81.2 ml of triethylamine and 102 g of tosyl chloride were added to the suspension, and the mixture was stirred at room temperature overnight. The reaction mixture was washed, dried and concentrated. To the residue was added diethyl ether and the precipitated crystals were collected by filtration to give 159 g of 1-(2-methylsulfanylpyrimidin-4- yl)ethanone-oxime tosylate. Melting point: 141-142°C.

(3) To 30 ml of methanol solution containing 12.9 g of 28% sodium methoxide-methanol was added dropwise 120 ml of a THF solution containing 15 g of the compound obtained in (2) under ice-cooling, and the mixture was stirred at room temperature overnight. To the mixture was added 100 ml of 4M hydrochloric acid-dioxane solution under ice-cooling, and after stirring at room temperature for 4 hours, the reaction mixture was concentrated. The residue was added to an aqueous potassium carbonate solution and extracted with chloroform. The organic layer was dried and concentrated, and the residue was purified by silica gel column chromatography (chloroform:methanol=15:1) to give 8.14 g of 2,2-dimethoxy-2-(2-methylsulfanylpyrimidin-4-yl)ethylamine.

(4) To 120 ml of a THF solution containing 8 g of the compound obtained in (3) was added dropwise under ice-cooling 30 ml of a THF solution containing 4.78 g of 4-fluorophenyl isocyanate, and the mixture was stirred at room temperature for 30 minutes. After 120 ml of conc. hydrochloric acid was added to the mixture under ice-cooling, the resulting mixture was stirred at room temperature overnight. Precipitated crystals were collected by filtration, washed with water and ether, and dried to give 7.35 g of 1-(4-fluorophenyl)-5-(2-methylsulfanylpyrimidin-4-yl)-4-imidazolin-2-one. Melting point: 260-261°C.

Reference example 6

[0194]

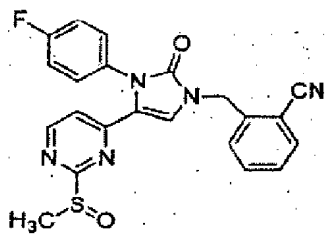


(1) To 40 ml of a DMF solution containing 2.6 g of the compound obtained in Reference example 5(4) was added 327 mg of sodium hydride at room temperature, and the mixture was stirred at room temperature for 30 minutes. To the mixture was added 1.77 g of 2-cyanobenzyl bromide, and after stirring at room temperature for 30 minutes, 33 mg of sodium hydride and 85 mg of 2-cyanobenzyl bromide were added to the mixture, and the resulting mixture was stirred at room temperature for an hour. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed, dried and concentrated, and crystallized from diethyl ether to give 3.28 g of 1-(2-cyanobenzyl)-3-(4-fluorophenyl)-4-(2-methylsulfanylpyrimidin-4-yl)-4-imidazolin-2-one. Melting point: 141-142°C.

(2) To a chloroform solution containing 3.27 g of the compound obtained in (1) was added 2.03 g of 3-chloroperoxybenzoic acid at room temperature, and the mixture was stirred at room temperature for an hour. To the reaction mixture was added 1.16 g of calcium hydroxide and the mixture was stirred at room temperature for 2 hours, and then, filtered through Celite, and the filtrate was concentrated. The residue was crystallized from ethyl acetate to give 2.39 g of 1-(2-cyanobenzyl)-3-(4-fluorophenyl)-4-(2-methylsulfinylpyrimidin-4-yl)-4-imidazolin-2-one. Melting point: 133-136°C.

Reference example 7

[0195]

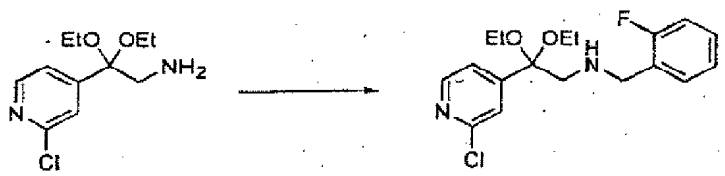


(1) To 150 ml of a methanol solution containing 1.47 g of the compound obtained in Reference example 5(4) was added dropwise 10 ml of an aqueous solution containing 1.79 g of Oxone® at room temperature. After 30 minutes and 2 hours, 2 ml of an aqueous solution containing 299 mg of Oxone® was added dropwise, and the mixture was stirred at room temperature for 2 hours. After removing insoluble matters by filtration, the filtrate was concentrated, an aqueous sodium bicarbonate solution was added to the concentrate and the mixture was extracted with chloroform. The organic layer was washed, dried and concentrated, and the precipitated crystals were collected by a mixed solvent of ethyl acetate-ether (1:1) to give 1.03 g of 1-(4-fluorophenyl)-5-(2-methylsulfinylpyrimidin-4-yl)-4-imidazolin-2-one. Melting point: 208-211°C (decomposed).

(2) The compound (930 mg) obtained in (1) was treated in the same manner as in the above-mentioned Reference example 6(1) to give 541 mg of 1-(2-cyanobenzyl)-3-(4-fluorophenyl)-4-(2-methylsulfinylpyrimidin-4-yl)-4-imidazolin-2-one.

Reference example 8

[0196]

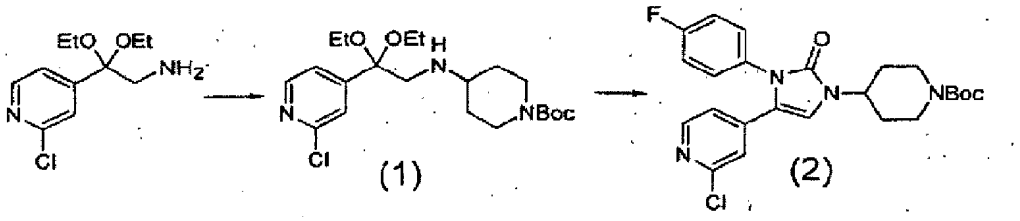


[0197] In 10 ml of methanol was dissolved 1.0 g of the compound obtained in Reference example 1(4), 0.51 g of 2-fluorobenzaldehyde was added to the solution, and the mixture was stirred at room temperature for 30 minutes. To the mixture was added 155 mg of sodium borohydride, and the resulting mixture was further stirred at room temperature for an hour. After concentration under reduced pressure, water was added to the reside and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous magnesium sulfate. After concentration

under reduced pressure, the residue was purified by silica gel column chromatography (hexane:ethylacetate=2:1) to give 1.45 g the title compound as an oily product.

Reference example 9

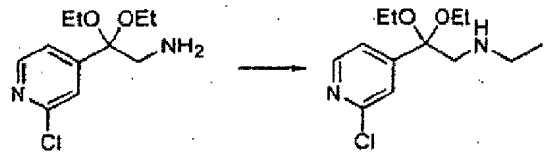
[0198]



[0199] The compound (5 g) obtained in Reference example 1.(4) and a corresopnding starting material were treated in the same manner as in Reference example 8 to give 8.47 g of Compound (1). Compound (1) (3 g) was treated in the same manner as in Example 1 to carry out cyclization, subsequently the resulting compound was dissolved in 20 ml of THF, 1.1 g of Boc_2O was added thereto. The resulting mixture was stirred at room temperature for 30 minutes, concentrated under reduced pressure and diisopropyl ether was added to the residue, and the residue was collected by filtration to give 2.53 g of Compound (2).

Reference example 10

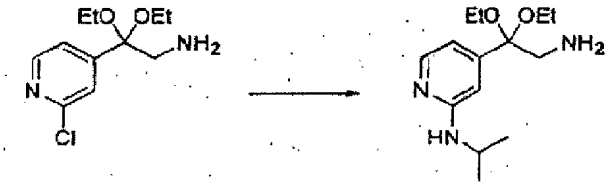
[0200]



[0201] A mixture comprising 3.8 g of the compound obtained in Reference example 1(4), 1.7 ml of ethyl iodide and 3.0 ml of triethylamine was stirred at 50°C overnight. After neutralizing with 2N aqueous NaOH solution, the reaction mixture was extracted with chloroform and dried over anhydrous magnesium sulfate. The resulting mixture was purified by NH silica gel column chromatography (hexane: ethyl acetate=4:1) to give 1.9 g of the title compound as an oily product.

Reference example 11

[0202]

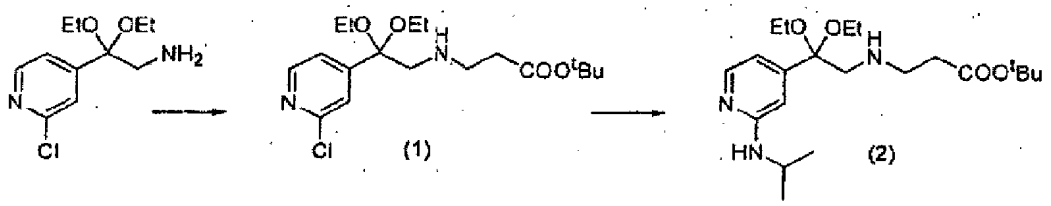


[0203] In 75 ml of toluene were suspended 5.0 g of the compound obtained in Reference example 1 (4), 35 ml of isopropylamine, 458 mg of palladium acetate, 1.28 g of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and 3.0 g of sodium t-butoxide, and under nitrogen flow, the mixture was stirred under heating at 70°C for 8 hours. After concentration under reduced pressure, water was added to the residue, and the mixture was extracted with chloroform, washed with

brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (chloroform:methanol= 10:1) to give 4.3 g of the title compound as an oily product.

Reference example 12

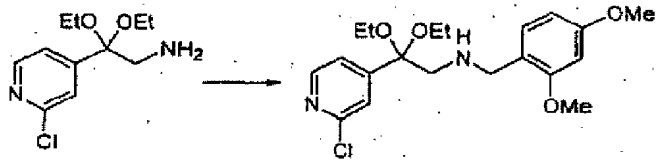
[0204]



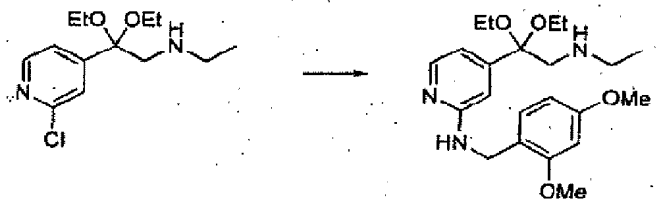
[0205] A mixture comprising 2.0 g of the compound obtained in Reference example 1(4), 0.82 mlof t-butyl acrylate and 10 ml of THF was stirred under reflux for 4 days. The reaction mixture was concentrated under reduced pressure to give 3.1 g of Compound (1) as an oily product. Then, Compound (1) and a corresponding starting material were treated in the same manner as in Example 4 to give 2.12 g of Compound (2) as an oily product.

Reference example 13

[0206]



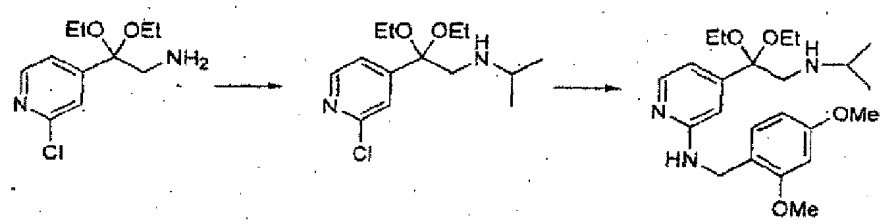
[0207] The compound (5.0 g) obtained in Reference example 1(4) was reacted with 2,4-dimethoxybenzaldehyde in the same manner as in Reference example 8 to give 6.4 g of the title compound. Reference example 14



[0208] The compound (1.39 g) of Reference example 10 was reacted with 2,4-dimethoxybenzylamine in the same manner as in Reference example 11 to give 1.58 g of the title compound.

Reference example 15

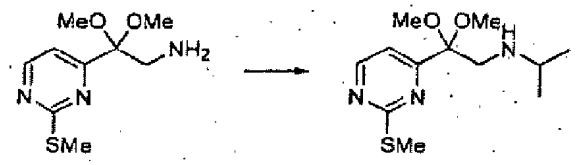
[0209]



[0210] The compound (10.0 g) of Reference example 1(4) was reacted with a corresponding starting material in the same manner as in Reference example 8, and then, reacted with 2,4-dimethoxybenzylamine in the same manner as in Reference example 11 to give 9.75 g of the title compound.

Reference example 16

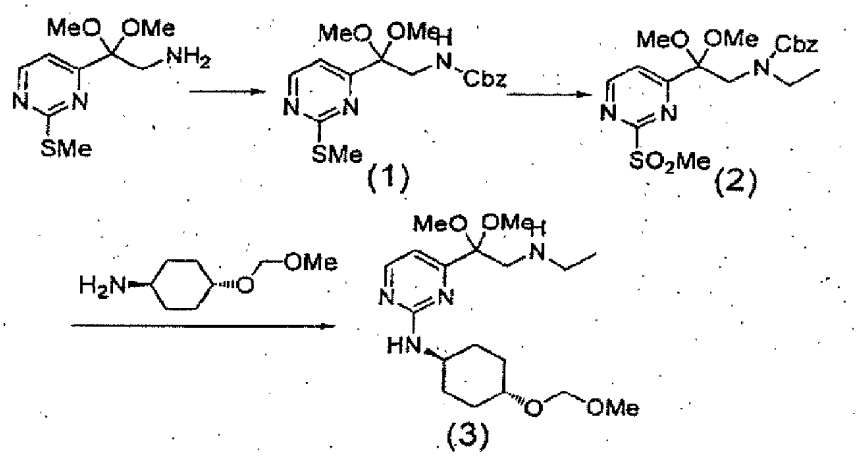
[0211]



[0212] The compound (26.8 g) of Reference example 5(3) and a corresponding starting material were treated in the same manner as in Reference example 8 to give 30.8 g of the title compound.

Reference example 17

[0213]



(1) In 30 ml of methylene chloride was dissolved 3.0 g of the compound of Reference example 5(3), 3.65 ml of triethylamine was added to the solution, and under ice-cooling, 3.35 g of benzyloxycarbonyl chloride was added dropwise to the mixture, and the mixture was stirred at room temperature overnight. The reaction mixture was washed with water and brine, and dried over anhydrous magnesium sulfate. After concentration under reduced

pressure, the residue was purified by silica gel column chromatography to give 2.23 g of Compound (1) as colorless crystals.
MS 364 ([M+H]+)
(2) In 17 ml of DMF was dissolved 4.2 g of Compound (1), and under ice-cooling, 528 mg of sodium hydride was added to the solution, and the mixture was stirred at room temperature for an hour. The mixture was again ice-cooled, 1.39 ml of ethyl iodide was added thereto, and the resulting mixture was stirred at room temperature for 30 minutes. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate, the extract was washed with water and brine, and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in 50 ml of chloroform, 6.26 g of 3-chloroperoxybenzoic acid was added to the mixture at room temperature, and the resulting mixture was stirred at the same temperature for 30 minutes. To the reaction mixture was added 2.58 g of calcium hydroxide and after stirring the mixture, the insoluble matters were removed by filtration. The filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography to give 4.55 g of Compound (2) as a colorless oily product.
MS 423 ([M+H]+)
(3) In 30 ml of dioxane was dissolved 2.19 g of Compound (2), 1.65 g of trans-4-(Methoxymethoxy)cyclohexylamine and 1.08 ml of 1,1'-diisopropylethylamine were added to the solution, and the mixture was stirred at 100°C for 14 hours. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate, washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography to give 2.0 g of a brownish oily product. This product was dissolved in 40 ml of methanol, 1 g of 10% palladium-carbon was added thereto, and the mixture was subjected to catalytic reduction under hydrogen pressure (2.7 atm) for 2 hours. Palladium was removed by filtration, and after concentration under reduced pressure, the residue was purified by NH silica gel column chromatography to give 1.04 g of Compound (3) as a brownish oily product.
MS 369 ([M+H]+)

Experimental Example 1 (pharmacological test)

Inhibition of lipopolysaccharide (LPS)-stimulated TNF-α production in mice in vivo

[0214] Tests were carried out to measure an inhibitory effects of the compounds of the present invention on LPS-stimulated TNF-α production in mice.

[0215] To Balb/cAnNCrj mice (6-8 weeks old, female, available from Japan Charlesriver, Co.) were administered test compounds (10 mg/kg, p.o.) dissolved in 0.5% methyl cellulose and 0.2% PEG-60 hydrogenated caster oil (HCO60, available from Nikko Chemicals, Co.). After 30 minutes, LPS (E. coli 0111:B4, available from Difco, with a final concentration of 1 mg/kg adjusted by phosphate buffered saline) was administered (0.4 ml/head, i.p.). 90 minutes later, blood was collected from abdominal vein of the mouse under diethyl ether anesthesia. The collected blood was subjected to centrifugation with 3000g to collect serum. TNF-α in the sera was measured by DuoSet mouse TNF-α ELISA kit (trade name, available from genzymeTECHNE).

[0216] As a result, the compounds of the present invention significantly reduced the production of TNF-α as shown in Table 52.

Table 52

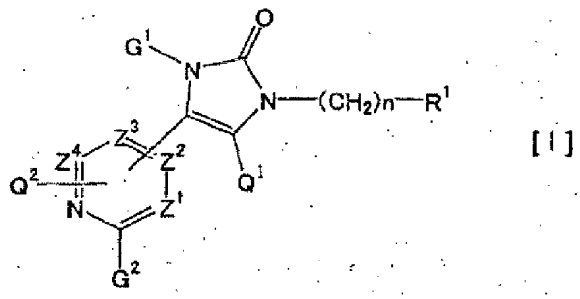
Examples	TNF-α inhibition rate
182	64%
202	57%
239	69%
296	52%
300	57%

Industrial Applicability

[0217] According to the present invention, a novel 4-imidazolin-2-one compound having excellent p38MAP kinase inhibitory activity, which is useful as a medicine, can be provided.

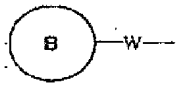
Claims

1. A compound of the formula [I]:



[I]

wherein G^1 is an alkyl which may be substituted by a halogen atom or an alkoxy, or a group of the formula:



wherein ring B is benzene ring, naphthalene ring, a monocyclic or bicyclic aromatic heterocycle or a cycloalkane, and the benzene ring, the naphthalene ring, the monocyclic or bicyclic aromatic heterocycle and the cycloalkane may be substituted by 1 to 3 substituent(s), which is(are) the same or different, and selected from the group consisting of a halogen atom, nitro, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted amino, an optionally substituted carbamoyl and cyano,

W is a single bond, or a c_1 - c_4 alkylene which may be substituted by 1 or 2 alkyl(s),

Q^1 and Q^2 may be the same or different, and each is hydrogen atom, a halogen atom or an alkyl,

n is 0, 1, 2, 3 or 4,

R^1 is hydrogen atom, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted phenyl or an optionally substituted heterocyclic group,

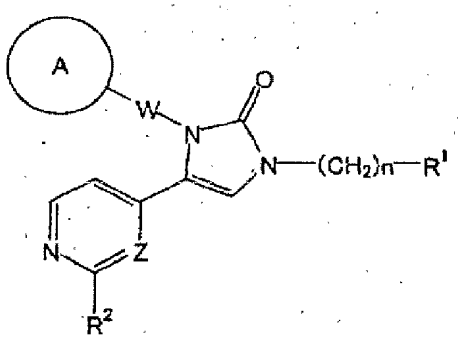
Z^1, Z^2, Z^3 and Z^4 may be the same or different, and each is CH or N, provided that 3 or more of Z^1, Z^2, Z^3 and Z^4 should not be N at the same time,

G^2 is hydrogen atom, $-NR^3R^4$, $-OR^5$, $-SR^5$ $-COR^6$, $-CHR^7R^8$, or a heterocyclic group,

where R^3 to R^8 each independently is hydrogen atom, an optionally substituted alkyl, an alkenyl, an alkynyl, hydroxy, an alkoxy, an optionally substituted amino, an optionally substituted alkanoyl, an optionally substituted carbamoyl, an alkoxyoxalyl, an alkylsulfonyl, an optionally substituted cycloalkyl, an optionally substituted phenyl, an optionally substituted heterocyclic group, a carbonyl substituted by an optionally substituted cycloalkyl, a carbonyl substituted by an optionally substituted phenyl or a carbonyl substituted by an optionally substituted heterocyclic group,

or a pharmaceutically acceptable salt thereof.

2. A compound of the formula [Ia]:



[Ia]

wherein ring A is benzene ring or a monocyclic aromatic heterocycle, and the benzene ring and the monocyclic aromatic heterocycle may be substituted by 1 to 3 substituent(s), which is (are) the same or different, and selected from the group consisting of a halogen atom, nitro, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted amino, an optionally substituted carbamoyl and cyano,
W is a single bond, or a c_1 - c_4 alkylene which may be substituted by 1 or 2 alkyl(s),
n is 0, 1, 2, 3 or 4,
R^1 is hydrogen atom, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted phenyl or an optionally substituted heterocyclic group,
Z is CH or N,
R^2 is hydrogen atom, $-NR^3R^4$, $-OR^5$, $-COR^6$ or $-CHR^7R^8$,
where R^3 to R^8, each independently is hydrogen atom, an optionally substituted alkyl, an alkenyl, an alkynyl, hydroxy, an alkoxy, an optionally substituted amino, an optionally substituted alkanoyl, an optionally substituted carbamoyl, an alkoxyoxalyl, an alkylsulfonyl, an optionally substituted cycloalkyl, an optionally substituted phenyl, an optionally substituted heterocyclic group, a carbonyl substituted by an optionally substituted cycloalkyl, a carbonyl substituted by an optionally substituted phenyl or a carbonyl substituted by an optionally substituted heterocyclic group,
or a pharmaceutically acceptable salt thereof.

3. The compound according to Claim 2, wherein the ring A is a benzene ring which may be substituted by 1 to 3 substituent(s), which is(are) the same or different, and selected from the group consisting of a halogen atom, nitro, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted amino and cyano, and W is a single bond, or a pharmaceutically acceptable salt thereof.

4. The compound according to Claim 2 or 3, wherein n is 0 or 1, or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of Claims 2 to 4, wherein n is 0 and R^1 is an optionally substituted alkyl, or n is 1 and R^1 is an optionally substituted cycloalkyl or an optionally substituted phenyl, or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of Claims 2 to 5, wherein R^2 is $-NR^3R^4$ or $-OR^5$, or a pharmaceutically acceptable salt thereof.

7. The compound according to any one of Claims 2 to 5, wherein R^2 is $-NHR^4$, and R^4 is an optionally substituted alkyl, an alkenyl, an optionally substituted alkanoyl, an optionally substituted carbamoyl, an optionally substituted cycloalkyl, an optionally substituted phenyl, an optionally substituted heterocyclic group, a carbonyl substituted by an optionally substituted cycloalkyl or a carbonyl substituted by an optionally substituted heterocyclic group, or a pharmaceutically acceptable salt thereof.

8. The compound according to Claim 2, wherein the ring A is a benzene ring which may be substituted by 1 or 2 substituent(s), which is(are) the same or different, and selected from the group consisting of a halogen atom, an optionally substituted alkyl, an optionally substituted alkoxy, an optionally substituted amino and cyano,
W is a single bond,
n is 0 or 1,
R^1 is hydrogen atom, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted

phenyl or an optionally substituted heterocyclic group,
Z is CH or N,
R^2 is hydrogen atom, $-NR^3R^4$, $-OR^5$, $-COR^6$ or $-CHR^7R^8$,
Where R^3 to R^8 each independently is hydrogen atom, an optionally substituted alkyl, an alkenyl, an alkoxy, an optionally substituted alkanoyl, an optionally substituted carbamoyl, an alkoxyoxalyl, an optionally substituted cycloalkyl, an optionally substituted phenyl, an optionally substituted heterocyclic group, a carbonyl substituted by an optionally substituted cycloalkyl or a carbonyl substituted by an optionally substituted heterocyclic group,
or a pharmaceutically acceptable salt thereof.

9. The compound according to Claim 2, wherein the ring A is a benzene ring which may be substituted by 1 or 2 substituent(s), which is(are) the same or different, and selected from the group consisting of a halogen atom, an alkyl, an alkoxy, an amino optionally substituted by alkyl(s) and cyano,
W is a single bond,
n is 0 or 1,
R^1 is

(1) hydrogen atom,
(2) an alkyl optionally substituted by group(s) selected from the group consisting of phenyl, an alkoxy, an alkylamino, a dialkylamino, an alkanoylamino, an alkylsulfonylamino, a carbamoyl optionally substituted by alkyl(s), hydroxy, carboxy and cyano,
(3) a cycloalkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (v):

(i) hydroxy,
(ii) an alkoxy optionally substituted by alkoxy(s),
(iii) an amino optionally substituted by group(s) selected from the group consisting of an alkyl', an alkanoyl and an alkylsulfonyl,
(iv) a carbamoyl optionally substituted by alkyl(s), and
(v) an alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, an alkoxy and amino,

(4) a phenyl optionally substituted by group(s) selected from the group consisting of the following (i) to (vi):

(i) a halogen atom,
(ii) an alkyl optionally substituted by group(s) selected from the group consisting of a halogen atom, hydroxy and phenylsulfonyl,
(iii) cyano,
(iv) an alkoxy,
(v) an amino optionally substituted by group(s) selected from the group consisting of an alkyl and an alkylsulfonyl,
(vi) a carbonyl substituted by a heterocyclic group, or

(5) a heterocyclic group optionally substituted by group(s) selected from the group consisting of the following (i) to (iv):

(i) an alkoxycarbonyl,
(ii) an alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, an alkoxy and a carbamoyl optionally substituted by alkyl(s),
(iii) an alkanoyl and
(iv) an alkylsulfonyl,

Z is CH or N,
R^2 is hydrogen atom, $-NR^3R^4$, $-OR^5$, $-COR^6$ or $-CHR^7R^8$,
where R^3 to R^8 each independently is:

(1) hydrogen atom,
(2) an alkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (vii):

(i) hydroxy,

(ii) an alkoxy,
(iii) an amino optionally substituted by group(s) selected from the group consisting of an alkyl, an alkanoyl and an alkylsulfonyl,
(iv) an alkoxycarbonyl,
(v) a cycloalkyl optionally substituted by group(s) selected from the group consisting of the following a) to g) :

a) hydroxy,
b) an amino optionally substituted by alkyl(s),
c) an alkanoylamino,
d) an alkylsulfonylamino,
e) an alkyl optioinally substituted by group(s) selected from the group consisting of hydroxy, an alkoxy, amino, a carbamoyl optionally substituted by alkyl(s),
f) carboxy and
g) a carbamoyl optionally substituted by alkyl(s),

(vi) a phenyl optionally substituted by group(s) selected from the group consisting of a halogen atom, an alkoxy and morpholinylcarbonyl, and
(vii) a heterocyclic group optionally substituted by alkyl(s),

(3) an alkenyl,
(4) an alkoxy,
(5) an alkanoyl optionally substituted by group(s) selected from the group consisting of the following (i) to (iv) :

(i) hydroxy,
(ii) an alkoxy,
(iii) an amino optionally substituted by group(s) selected from the group consisting of an alkyl and an alkanoyl,
(iv) an alkoxycarbonyl,

(6) a carbamoyl optionally substituted by alkyl(s),
(7) an alkoxyoxalyl,
(8) a cycloalkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (vii):

(i) a halogen atom,
(ii) hydroxy,
(iii) an alkoxy,
(iv) an amino optionally substituted by group(s) selected from the group consisting of an alkyl, an alkanoyl, an alkoxycarbonyl and an alkylsulfonyl,
(v) an alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, an alkoxy, amino, a carbamoyl optionally substituted by alkyl(s),
(vi) an alkanoyloxy and
(vii) a carbamoyl optionally substituted by alkyl(s),

(9) a phenyl optionally substituted by group(s) selected from the group consisting of a halogen atom and an alkoxy,
(10) a heterocyclic group optionally substituted by group(s) selected from the group consisting of the following (i) to (v):

(i) an alkyl optionally substituted by group(s) selected from the group consisting of phenyl, hydroxy, an alkoxy, amino and a carbamoyl optionally substituted by alkyl(s),
(ii) an alkoxycarbonyl,
(iii) an alkanoyl,
(iv) an alkylsulfonyl,
(v) oxo

(11) a carbonyl substituted by a cycloalkyl optionally substituted by group(s) selected from the group consisting of hydroxy, amino and an alkanoylamino, or

(12) a heterocyclic group-substituted carbonyl,

or a pharmaceutically acceptable salt thereof.

10. The compound according to Claim 2, wherein the ring A is a benzene ring which may be substituted by 1 or 2 substituent(s), which is(are) the same or different, and selected from the group consisting of fluorine atom, chlorine atom, an alkyl and an alkoxy,
W is a single bond,
n is 0 or 1,
R^1 is

(1) hydrogen atom,
(2) an alkyl optionally substituted by group(s) selected from the group consisting of phenyl, an alkoxy, an alkylamino, a dialkylamino, an alkanoylamino, an alkylsulfonylamino, a carbamoyl optionally substituted by alkyl(s), hydroxy, carboxy and cyano,
(3) a cycloalkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (v):

(i) hydroxy,
(ii) an alkoxy optionally substituted by alkoxy(s),
(iii) an amino optionally substituted by group(s) selected from the group consisting of an alkyl, an alkanoyl and an alkylsulfonyl,
(iv) a carbamoyl optionally substituted by alkyl(s),
(v) an alkyl optionally substituted by group(s) selected from the group consisting of hydroxy and amino,

(4) a phenyl optionally substituted by group (s) selected from the group consisting of the following (i) to (iv):

(i) a halogen atom,
(ii) an alkyl optionally substituted by halogen atom(s),
(iii) cyano, and
(iv) an alkoxy, or

(5) a heterocyclic group,

Z is CH or N,
R^2 is hydrogen atom, $-NR^3R^4$, $-OR^5$, or $-COR^6$,
Where R^3 to R^6 each independently is:

(1) hydrogen atom,
(2) an alkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (vi):

(i) hydroxy,
(ii) an alkoxy,
(iii) an alkoxycarbonyl,
(iv) a cycloalkyl optionally substituted by group(s) selected from the group consisting of the following a) to e):

a) hydroxy,
b) an amino optionally substituted by alkyl(s),
c) an alkanoylamino,
d) an alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, amino and a carbamoyl optionally substituted by alkyl(s), and
e) a carbamoyl optionally substituted by alkyl(s),

(v) a phenyl optionally substituted by alkoxy(s), and
(vi) a heterocyclic group,

(3) an alkenyl,
(4) an alkoxy,

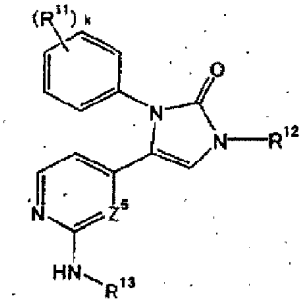
(5) an alkanoyl optionally substituted by group(s) selected from the group consisting of an alkoxy, an amino optionally substituted by alkanoyl(s), and an alkoxycarbonyl,
(6) a cycloalkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (v):

(i) hydroxy,
(ii) an alkoxy,
(iii) an amino optionally substituted by group(s) selected from the group consisting of an alkyl, an alkanoyl, an alkoxycarbonyl and an alkylsulfonyl,
(iv) an alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, amino and a carbamoyl optionally substituted by alkyl(s),
(v) a carbamoyl optionally substituted by alkyl(s),

(7) a heterocyclic group optionally substituted by group(s) selected from the group consisting of an alkyl optionally substituted by phenyl(s) and an alkoxycarbonyl,
(8) a carbonyl substituted by a cycloalkyl optionally substituted by group(s) selected from the group consisting of hydroxy and amino, or
(9) a heterocyclic group-substituted carbonyl,

or a pharmaceutically acceptable salt thereof.

11. A compound of the formula [Ib]:



wherein R^{11} is a group selected from the group consisting of hydrogen atom, a halogen atom, a c_1 - c_4 alkyl, and a c_1 - c_4 alkoxy,
k is 1 or 2, and when k is 2, two of R^{11}s may be the same or different,
R^{12} is

(1) a c_1 - c_4 alkyl,
(2) a c_3 - c_4 cycloalkylmethyl,
(3) carbamoylmethyl, or
(4) a benzyl optinally substituted by group(s) selected from the group consisting of cyano, a halogen atom, a c_1 - c_3 alkoxy, a c_1 - c_3 alkyl and a halogen-substituted c_1 - c_3 alkyl,

Z^5 is CH or N,
R^{13} is

(1) a c_1 - c_6 alkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (iii):

(i) a c_5 - c_7 cycloalkyl optionally substituted by group(s) selected from the group consisting of the following a) to e):

a) hydroxy
b) an amino optionally substituted by c_1- c_4 alkyl(s),
c) a c_1 - c_4 alkanoylamino,
d) a c_1 - c_4 alkyl optionally substituted by group(s) selected from the group consisting of hydroxy,

amino, and a carbamoyl optionally substituted by c_1 - c_4 alkyl(s), and
e) a carbamoyl optionally substituted by c_1 - c_4 alkyl(s),

(ii) hydroxy, and
(iii) a carbamoyl optionally substituted by c_1 - c_4 alkyl (s), or

(2) a c_5 - c_7 cycloalkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (iii):

(i) hydroxy,
(ii) a c_1 - c_4 alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, amino and a carbamoyl optionally substituted by c_1 - c_4 alkyl(s), and
(iii) a carbamoyl optionally substituted by c_1 - c_4 alkyl(s),

or a pharmaceutically acceptable salt thereof.

12. The compound according to Claim 11, wherein R^{11} is a group selected from the group consisting of hydrogen atom, fluorine atom, chlorine atom, methyl and methoxy,
k is 1 or 2, and when k is 2, two of R^{11}s may be the same or different,
R^{12} is a c_1 - c_4 alkyl, cyclopropylmethyl or carbamoylmethyl, or a pharmaceutically acceptable salt thereof.

13. The compound according to Claim 11, wherein R^{11} is hydrogen atom or fluorine atom,
k is 1,
R^{12} is ethyl, isopropyl, isobutyl, cyclopropylmethyl or carbamoylmethyl,
R^{13} is

(1) a c_1 - c_6 alkyl optionally substituted by group(s) selected from the group consisting of the following (i) and (ii):

(i) a c_5 - c_7 cycloalkyl optionally substituted by group(s) selected from the group consisting of hydroxy, a hydroxy c_1 - c_4 alkyl and a carbamoyl optionally substituted by c_1 - c_4 alkyl(s), and
(ii) hydroxy, or

(2) a c_5 - c_7 cycloalkyl optionally substituted by group(s) selected from the group consisting of the following (i) to (iii):

(i) hydroxy,
(ii) a c_1 - c_4 alkyl optionally substituted by group(s) selected from the group consisting of hydroxy, amino and a carbamoyl optionally substituted by c_1 - c_4 alkyl(s),
(iii) a carbamoyl optionally substituted by c_1 - c_4 alkyl(s),

or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/10937

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D401/04, 401/14, 403/04, 403/14, 405/14,
409/14//A61K31/4439, 31/444, 31/4545, 31/496, 31/506,
A61P1/00, 1/04, 1/16, 3/10, 9/00, 9/10, 11/00, 11/02,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D401/04, 401/14, 403/04, 403/14, 405/14,
409/14//A61K31/4439, 31/444, 31/4545, 31/496, 31/506,
A61P1/00, 1/04, 1/16, 3/10, 9/00, 9/10, 11/00, 11/02,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS, REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 85/02402 A1 (American Hospital Supply Corp.), 06 June, 1985 (06.06.85), & US 4532250 A & CA 1258072 A & AU 8436783 A & EP 162102 A1 & JP 61-500494 A	1
X	US 3538104 A (Geigy Chem. Corp.), 03 November, 1970 (03.11.70), & DE 2009408 A & NL 7002463 A & CH 526566 A & BE 746656 A & FR 2034575 A & ES 376965 A & BR 7017105 A & GB 1305273 A	1
X	J.Med.Chem., (1999), 42(14), p.2706-15	1
X	Proceedings NOBCCHE, (1994), 21, p.101-15	1

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 November, 2002 (19.11.02)	24 December, 2002 (24.12.02)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/10937

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96/21452 A1 (SmithKline Beecham Corp.), 18 July, 1996 (18.07.96), & ZA 9600094 A & AU 9646572 A & US 5593992 A & US 5663334 A & NO 9703167 A & BR 9606904 A & FI 9702901 A & EP 809499 A1 & SK 9700902 A & CZ 9702158 A & KR 98701278 A & NZ 301204 A & HU 9702409 A & US 6103936 A & IL 116455 A & IL 134324 A & IL 134322 A & CN 117299 A & IL 134323 A & NO 200106225 A & NO 200106226 A & JP 10-512555 A & JP 2002-105047 A	1-13
A	WO 96/21654 A1 (SmithKline Beecham Corp.), 18 July, 1996 (18.07.96), & AU 9647704 A & ZA 9600156 A & NO 9703231 A & EP 802908 A1 & FI 9702970 A & BR 9607097 A & CZ 9702195 A & JP 10-512264 A & KR 98701374 A & NL 302117 A & HU 200102677 A	1-13
A	WO 96-40143 A1 (SmithKline Beecham Corp.), 19 December, 1996 (19.12.96), & AU 9662726 A & ZA 9604723 A & NO 9705716 A & EP 831830 A1 & CZ 9703925 A & BR 9608591 A & HU 9802259 A & JP 11-513017 A & KR 99022574 A & NZ 311403 A & US 6218537 B1 & IL 118544 A & TW 442481 A & CN 1192147 A	1-13
A	WO 00/64894 A1 (Takeda Chem. Ind., Ltd.), 02 November, 2000 (02.11.00), & AU 200038401 A & JP 2001-114779 A & NO 200105156 A & EP 1180518 A1 & BR 200009952 A & CZ 200103805 A & SK 200101495 A & KR 2001111314 A & CN 1353710 A	1-13
A	WO 99/01449 A1 (Novartis A.G.), 14 January, 1999 (14.01.99), & ZA 9805656 A & AU 9888015 A & NO 9906429 A & EP 993456 A1 & CZ 9904741 A & SK 9901865 A & BR 9810955 A & CN 1261885 A & JP 2001-506280 A & HU 200003351 A & KR 2001013215 A & TW 429258 A & US 6300347 B1 & NZ 501275 A	1-13

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/10937

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/03837 A1 (Ortho-Mcneil Pharm. Inc.), 28 January, 1999 (28.01.99), & AU 9887570 A & US 6040320 A & EP 994858 A1 & KR 2001014288 A & JP 2002-515915 A	1-13

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/10937

Continuation of A. CLASSIFICATION OF SUBJECT MATTER
(International Patent Classification (IPC))

Int.Cl[7] 11/06, 13/12, 17/00, 17/02,17/04, 17/06, 19/00, 19/02, A61P19/06, 19/10, 25/16, 15/28, 27/02, 29/00, 31/18, 35/00, 43/00

(According to International Patent Classification (IPC) or to both national classification and IPC)

Continuation of B. FIELDS SEARCHED
Minimum Documentation Searched(International Patent Classification (IPC))

Int.Cl[7] 11/06, 13/12, 17/00, 17/02,17/04, 17/06, 19/00, 19/02, A61P19/06, 19/10, 25/16, 15/28, 27/02, 29/00, 31/18, 35/00, 43/00

Minimum documentation searched (classification system followed by classification symbols)

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